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Synthesis of Fluroxypyr for the Use on Broad Leaf Plants

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Synthesis of fluroxypyr – for the use on broad leaf plants

By

Shena Ruane

This work was carried out in the Department of Chemistry in Dublin Instituted of Technology, Kevin Street, Dublin 8 under the supervision of Dr. P Mulligan and in Argiguard Ltd., Chemistry Department Dublin City University, Glasnevin, Dublin 7 under the direction of Dr. Nigel McSweeney and Mr Brian Parker.

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May 2000

Declaration page

I certify that this thesis which I now submit for examination for the award of MPhil, is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

This thesis was prepared according tot he regulations for postgraduate studies by research of the Dublin Institute of technology and has not been submitted in whole or in part for an award in any other Institute or University.

Signature _____ Date 4-12-00

Candidate

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Table of contents:

Abstract

Fluroxypyr, 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate is used for the control of annual broad leaf weeds in cereals and perennial rye grass. The objective of this work was to develop an economically viable process for the bench synthesis of an organic herbicide fluroxypyr and to scale up the reaction to two litres. This was carried out according to a technical bulletin received from Agriguard Ltd. In addition an investigation into the synthesis and characterisation of impurities formed and reported to be formed, in the reaction process was carried out.

The process developed began with pentachloropyridine which on reaction with potassium fluoride in an aprotic dipolar solvent yielded 3,5-dichloro-2,4,6-trifluoropyridine. This was then subjected to ammonation followed by hydrolysis to yield potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate. This was then alkylated to yield methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate, which was then converted to 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate fluroxypyr. The yield of fluroxypyr produced was 47.89% with respect to pentachloropyridine.

An alternative method for the synthesis of fluroxypyr was also investigated and the process developed had the first two stages the same as described above. The final stage of this alternative synthesis involved the preparation of fluroxypyr by the alkylation of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate with methylheptyl chloroacetate. The overall yield for this alternative method with respect to pentachloropyridine was 40.96%. Methylheptyl chloroacetate is not commercially available and was prepared in a 65.5% yield from 2-octanol and chloroacetic acid.

Chapter 1

Introduction

1.1 Herbicides- A general introduction:

Man first domesticated plants and animals about 10,000 years ago and this is probably the most significant single occurrence in human history[1]. This was the beginning of farming and the population at this time was about 3 million. Due to the success of man domesticating plants it has led to over a 1000-fold increasc in the numbers of mankind. Mankind's further welfare is dependent on his continuing success and ability to control plant growth, as all animal life depends on plants. Due to the ever increasing population (5.9 billion in 1998 and expected to rise to 6.8 billion by 2008) the demand for food is increasing and this is where herbicides become important. If all these people are to be fed, the production, quality and yields of crops must be increased. A herbicide is by definition a 'chemical formulation which is used to remove unwanted vegetation (weeds) from the desired crop'[2].

A weed is by definition a plant growing where it is not wanted[3]. Most of the modern weeds did not exist before agriculture. A frequently asked question is why do we have weeds? And the answer to this is probably that the crops which man produces must be compatible to the climatic conditions of that region. Thus we have regions or "belts" which produce certain crops such as corn, wheat, rice, fruits, lumbers etc. This type of monoculture favours the invasion of weeds for a number of reasons; (1) crops arc usually sown in rows leaving gaps that are available for colonisation by other species; (2) crops are usually grown in pure strands, a single species generally fails to truly exploit the habitat.

Crops to us may be weeds in the future when these plants, that is non-essential crops (tea, tobacco etc.), arc replaced with essential crops (wheat, corn, rice etc.), to feed the hungry. Weeds compete with crops for light, nutrients, water and spacc. More water and nutrients are needed to raise a ton of weeds than to raise a ton of most crops. Weeds when young characteristically exhibit rapid spreading and deeply penetrate their root systems giving them an early advantage in obtaining water and nutrients[1].

Weeds cause greater loss to crop production than either insects or plant diseases[1]. Weeds not only cause losses by competing for water, space, and nutrients but also cause loss by increasing the cost of harvesting. Damage to machinery or clogging of harvesting equipment may occur when substantial strands of old prennial weeds or brush are cut. This may necessitate a delay, for the cleaning and repair of equipment.

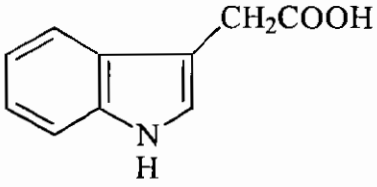
Some weeds are poisonous to stock for example *oenanthe crocata* (dropwort). Other weeds like wild onion and wild garlic, bitterweed (*Actinea odorata)* cause serious problems in dairy areas by giving an off-flavour to milk.

Weeds of waterways cause enormous losses of water. In irrigated areas they reduce the stream flow, cause silt deposition, and give protection to rodents which burrow in the bank. Boat transport is sevcrely limited by aquatic weeds, for example algae and *enchhornia crassipes* (water hyacinth) clog up tropical canals[3]. Fishing, swimming and recreation may be almost curtailed by weed growth. Weeds are also dangerous and may cause serious accidents when found growing on and around railway tracks and roadsides.

Poisonous plants also affect human health, for example contact with poison ivy, poison oak or poison sumac can cause considerable distress.

Originally weeds were controlled by hand, using pointed sticks, metal hoes or machetes, then with the domesticating of animals, the horse or oxen and plough were used. These methods are still in use but weed control was simplified with the invention of the combustion engine, which led to the development of the tractor and other farming equipment. This led to a dramatic change in agricultural methods and a 50% reduction of the time spent in growing crops and controlling weeds. The mechanical revolution was probably the main factor in revolutionising agricultural methods but the discovery of herbicidal active chemicals both inorganic and organic has further revolutionised agriculture. Inorganic chemicals such as copper salts, sulphuric acid and arsenic compounds were used in the late 19^{th} and early 20^{th} century.

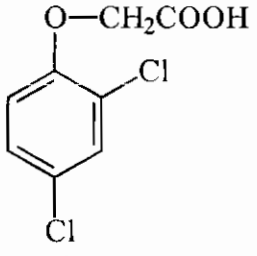
The discovery of the phenoxyacetic acid herbicides in the 1940's was a major breakthrough in the selective control of weeds. The development of the phenoxyacetic acid herbicides started as far back as 1881 with work done by Charles Darwin[4]. At this time a scientist called Sachs reported that 'chemical messengers' were related to flowering behaviour of beganas and squash. This chemical messenger (plant hormone) was isolatcd and eventually identified as indoleactic acid **(1)**[1] (figure 1.1.1).



(1)

Figure 1.1.1

A plant hormone or plant growth regulator is an organic compound, other than nutrients, that in low concentrations affects the morphological structure and /or physiological process of plants. There are a number of different types of plant hormones, for example auxins, gibberellins, cytokinins and ethylene. When indoleactic acid was synthesised, it was discovered that its application externally could cause dramatic effects on plant growth. This led to the investigation and manufacture of related compounds the most important of these from a herbicidal point of view was 2,4-dichlorophenoxyacetic acid **(2)** (figure 1.1.2). That was first synthesised in 1941 and first applied in field trials in 1944. It is classed as an auxin-type herbicide[5].



(2)
2,4-dichlorophenoxy acetic acid
(2,4-D)

Figure 1.1.2

1.2 Plant physiology

1.2.1 General introduction

In order to understand how a herbicide works, it is necessary to first have an understanding of the plant (weed) which is to be controlled. To understand what constitutes a plant and how it grows.

The Cell: Plants are multicellular organisms consisting of millions of cells with specialised functions[6]. These cells show a wide variation in size and shape but they have a common organisation. All plants contain a nucleus, cytoplasm and subcellular organelles, all of which are enclosed by a membrane to form the protoplasm (figure 1.2.1)[6].

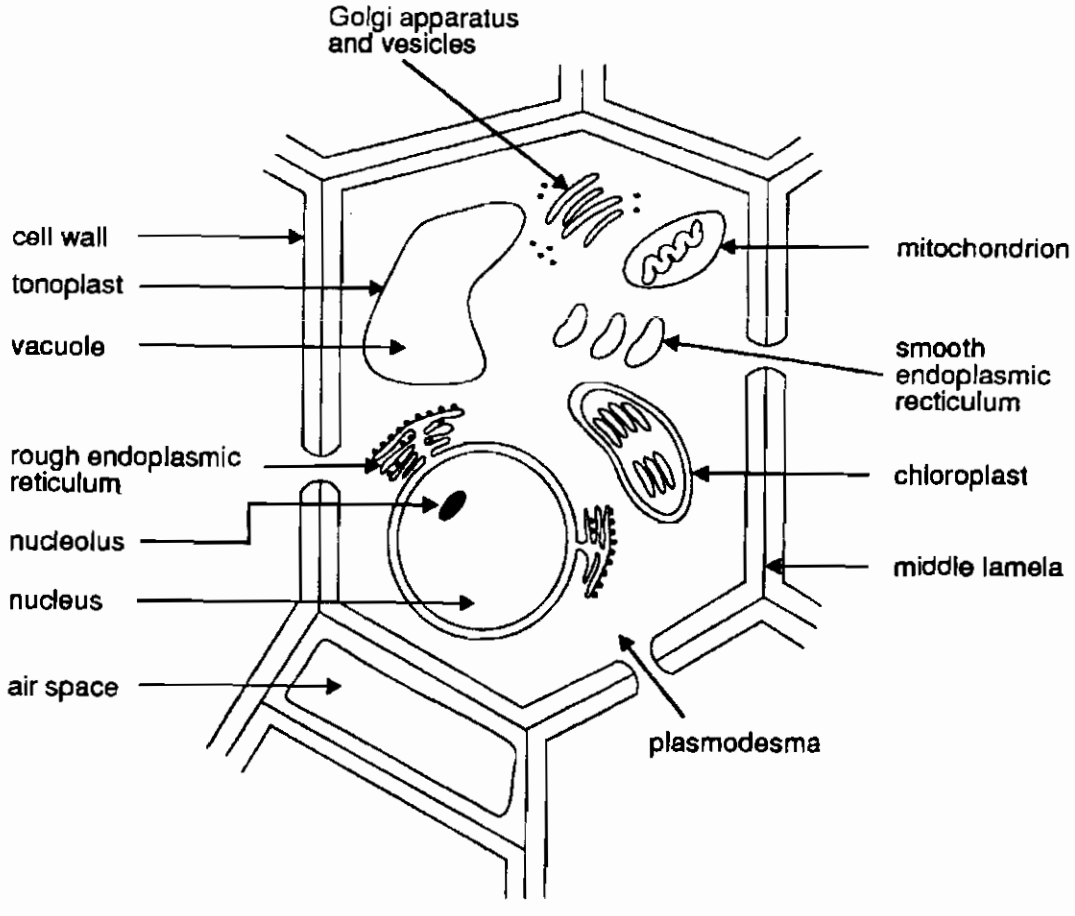


Figure1.2.1[6] Diagrammatic representation of a typical plant cell.

The nucleus usually consists of a nucleolus, chromosomes and a nuclear membrane. The subcellular organelles consists of the endoplasmic reticulum, mitochondria, ribosomes, golgi bodies, chloroplasts, vacuoles, pigments and granules. The cell is enclosed by a cell membrane or a plasma membrane and the cell wall. The cell wall and chloroplast are unique to the plant cells. The chloroplast is by far the largest plant cell organelle after the nucleus. The major metabolic processes of the plant photosynthesis takes place in the chloroplast. The chloroplasts are not found in all plant tissues but are limited to thin-walled cells chiefly in the mesophyll of leaves, in the outer cortical cells of herbaceous stem, in some aerial roots and in cells of similar types in lower plants. The chloroplast is bound by a limiting membrane and contains three membrane-bound compartments, the envelope intermembrane space, the stroma and the grana (figure 1.2.2)[7].

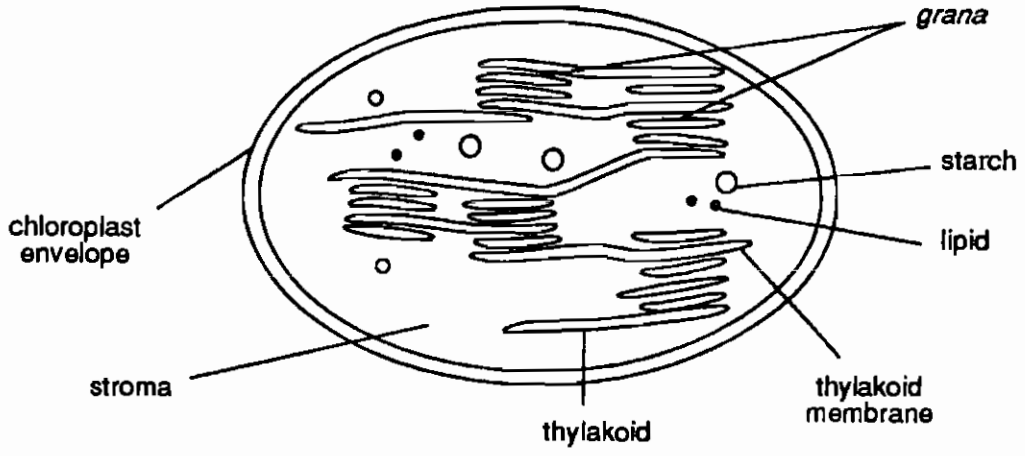


Figure 1.2.2 Shows a stylised transverse section of a chloroplast

The grana consist of internal membranes called thylakoids. These form flattened sacs which run parallel with the long axis of the chloroplast and in places are stacked up on top of one another. The space around the thylakoids in the chloroplast is filled with a fluid called the stroma. The stroma contains dissolved salts and enzymes. Chlorophyll molecules are found within the grana and the arrangement of the thylakoids is ideal for absorbing light and utilising it in photosynthesis.

Plants basically consist of leaves, a stem and a root. The stem and leaves together are called the shoot. The position of attachment of each leaf to the stem is termed an internode. The shoot is generally found above ground. Along with the leaves

and nodes the stem also consists of buds, flowers and fruits. Young green stems and leaves are the main sites for photosynthesis in the plant. The root system is generally found below ground. The roots main functions are anchoring the plant and the absorption of minerals from the soil. The roots can also serve as storage organs for the deposition of starch, water and other substances.

Plants are composed of three main tissue (a) dermal tissues; (b) ground tissues, (c) vascular tissues. A tissue consists of a number of cell types, which usually co-operate in a single function. *Dermal tissue* can be found in young plants and the main section of older plants. Dermal tissues comprise the surface cells of plants. In young plants the single-celled outer layer of dermal tissue is called the epidermis. In older plants the original epidermis gets replaced by bark, which strictly speaking is not dermal tissue. *Ground tissue* makes up the bulk of young plants. Three different types of cells are found in ground tissue; parenchyma, collenchyma and sclerenchyma, of these parenchyma are most abundant. Parenchyma cells function as packing cells, which fill the spaces between other tissues and also carry out most of the metabolic activities of the plant. Parenchyma cells in the leaves are characterised by the presence of large numbers of chloroplasts and these cells are sometimes referred to as chlorenchyma. Parenchyma cells are thin walled and are usually 15μm wide by 30-40μm long. Collenchyma cells differ from the thin-walled parenchyma cells in having primary walls that are thickened with lignin. Sclerenchyma cells are of two types; fibres and sclereids. Fibres, which are elongated, typically occur in strands or bundles. Sclerenchyma walls are also thickened with lignin. Both sclerenchyma and collenchyma have structural roles within the plant.

The third tissue type the vascular tissue consists of specialised conducting cells (xylem and phloem), supporting fibres and parenchyma cells, which store food and water. Xylem is the vascular tissue concerned with water and mineral transport whereas the phloem cells transports the products of photosynthesis and a number of other organic compounds. Xylem is made up of two types of conducting cells, the tracheids and vessel membranes, both of which are dead cells, as they have no cytoplasm or nucleus when mature. Xylem walls are impregnated with lignin in a number of different forms. Although these cells are dead they are still capable of functioning as a conducting unit. The tracheids are long, thin cells that overlap with one another on their tapered ends. These overlapping surfaces contain thin areas and pits. Water passes

from one tracheid to the next through the pits. Vessel members are much larger than tracheids. Vessel members form a continuous vessel, which is a more effective conduit than a series of tracheids.

The specialised cells of the phloem are called sieve tubes. A sieve tube is a vertical column of sieve-tube members joined by their end walls. These end walls are called sieve plates, having an opening leading from one sieve tube member to the next. There are similarities between sieve tubes and xylem vessels, however one major difference is that sieve tube cells are living cells. However during their development, their nuclei degenerate and their metabolism is considered to be directed by the nucleus of a companion cell, a cell type normally found in close association with a sieve tube cell. Companion cells are responsible for the active secretion of substances into and out of the sieve-tube member and are thought to fulfil their energy requirements. A sieve-tube member and its companion cell arise from the same mother cell. When xylem and phloem are found together it is known as a vascular bundle, with xylem on the inside and phloem on the outside, divided by a layer of reproducing cells called vascular cambium.

1.2.2 Parts of the plant-leaf, stem and root

An understanding of the leaf structure and its functions are needed in order to understand how a foliage-applied herbicide is absorbed.

Leaf structure.

The leaf is a compromise between two conflicting evolutionary pressures. The leaf must expose a maximum photosynthetic surface to sunlight and secondly it must control water evaporation. The basic structure of a leaf may be divided into three main area (figure 1.2.3)[8].

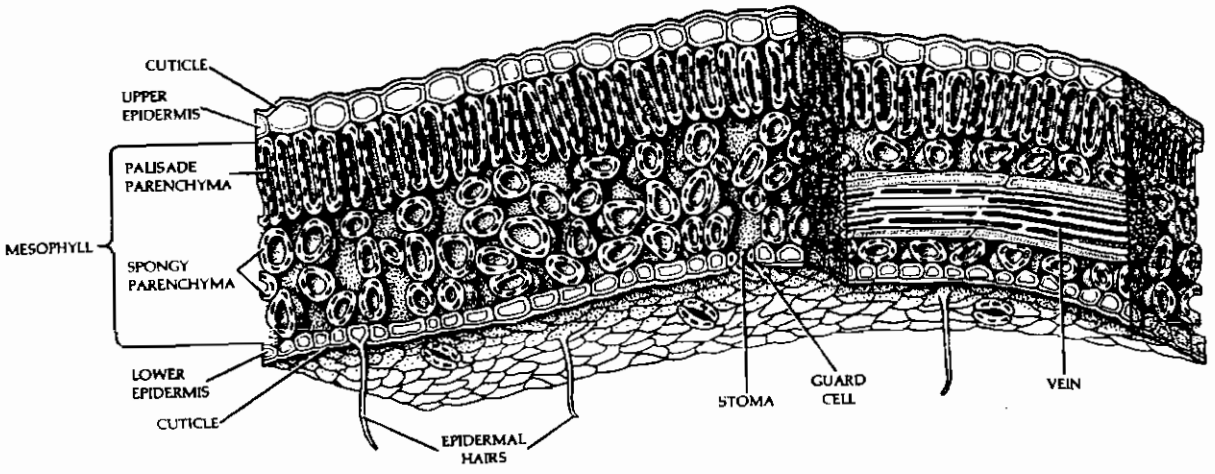


Figure 1.2.3 Diagram of the interior of a leaf.

1) The epidermis which consist of the upper and lower layers of the leaf, the latter containing stomata and epidermal hair.
2) The mesophyll consisting of parenchyma (palisade and spongy).
3) The veins consisting of the phloem and xylem (vascular bundles).

The mesophyll or 'middle leaf' makes up the bulk of the leaf. The upper layer is made up of palisade cells and chloroplasts can be found in the mesophyll region. The mesophyll is completely enclosed in an almost airtight cover made up of epidermal cell, which secrete a waxy substance called cutin. The cutin forms the cuticle, which is a coating over the epidermal cells. The epidermis and cuticle are transparent, allowing light to penetrate to the chloroplast the site of photosynthesis. Openings in the epidermis, the stomata, permit the exchange of gases.

The veins supply water and minerals to the leaf cells via the vascular bundles. The xylem transports water and minerals to the epidermis and mesophyll. The phloem transport sugars, usually in the sucrose form and other products carried in water from the photosynthetic cells to the other cells in the plant, that is to the stem, roots and branches.

The stem holds the leaves up to the light and provides transportation of substances to and from the leaves and roots. The outer surface is made up of epidermal cells and covered with a waxy cuticle. The other tissues of the stem are cortical parenchyma (ground tissue); vascular bundles consisting of phloem and xylem (vascular bundles) and pith see figure 1.2.4[8].

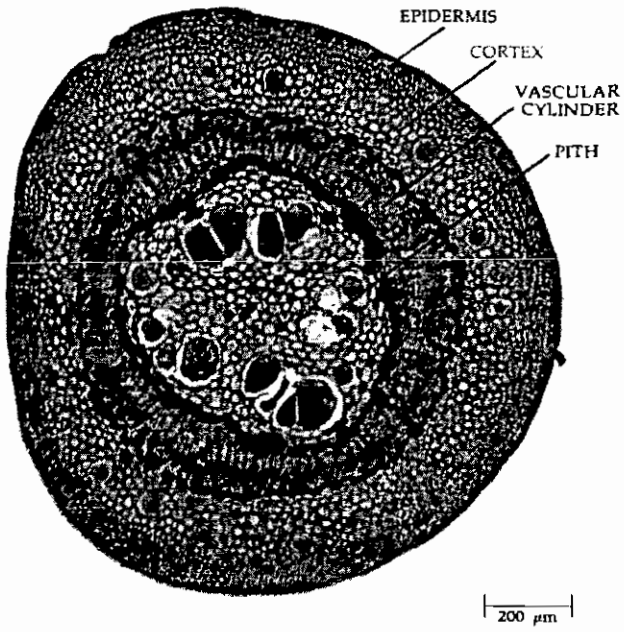


Figure 1.2.4 A cross section of a dicot stem

The roots of a plant are specialised structures that anchor the plant and take up water and essential minerals. In the root the three tissues (dermal, ground and vascular) are arranged in three concentric layers: the epidermis, the cortex and the vascular cylinders, see figure 1.2.5[8]. The epidermis encloses the surface of the roots and absorbs water and minerals from the soil and also protects the internal tissues. Root hairs are slender extensions of the epidermal cells. Root hairs assist in the absorption of water and minerals. The cortex occupies the greatest volume of the root. The cortex cells are parenchyma cells, which lack chloroplast but contain starch and other organic substances. There are many air spaces in the cortex. Unlike the rest of the cortex the cells of the endodermis are compact and have no air spaces between them. A casparian strip encircles each endodermal cell. A casparian strip is a waxy band within the cell wall see figure 1.2.6[8]. The strip is continuous and is not permeable to water. This membrane regulates the passage of substances into the vascular bundles. The vascular cylinders of the roots consist of the vascular bundles completely surrounded by one or more layers of cells, the pericycle. The vascular tissues of the root are continuous with those of the stem

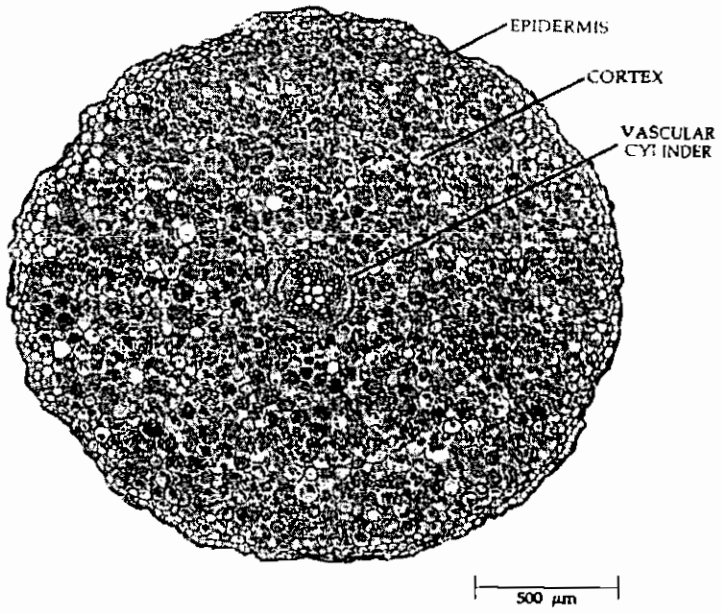


Figure 1.2.5[8] A cross section of a dicot root

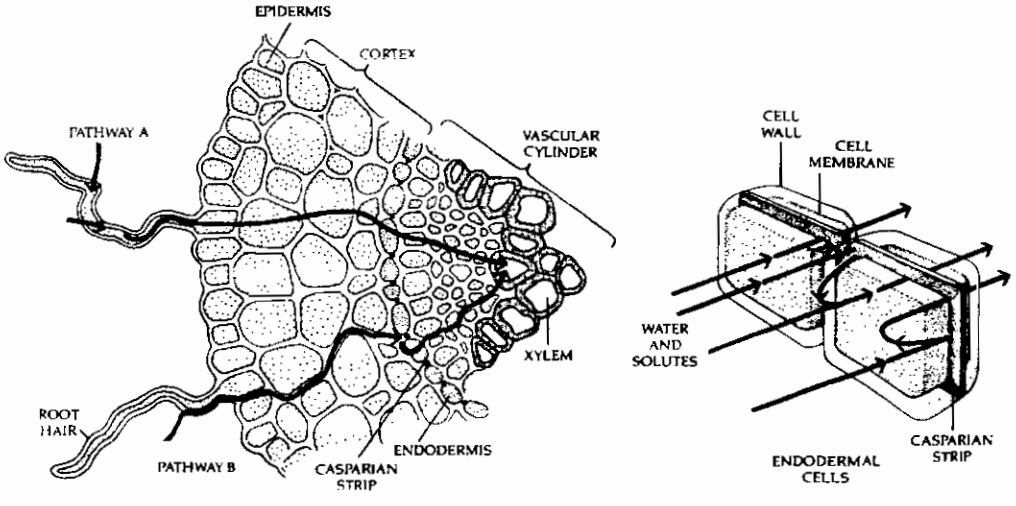


Figure 1.2.6[8] A Diagrammatic cross section of a root, showing the two pathways of uptake of water and dissolved substances

1.2.3 Symplasm and apoplasm pathways of transport

As previously mentioned the xylem and the phloem tissues are the transport system for the plant and are present in the roots, leaf and stems of plants. Translocation in plants is generally considered to be the upward movement of aqueous solution in the xylem and of the downward movement of organic compounds in the phloem. However sugars which are produced in mature leaves can be carried upwards by the phloem to the growing apex, flowers, fruits and young leaves.

There are two important transportation routes within plant tissue, the symplasm and apoplasm pathways. The symplast can be defined as " the total mass of living cells of a plant connected throughout the plant by the plasmodesmata"[9]. The symplasm refers to everything bounded by the plasmalemma (cell membrane) except the vacuoles. The apoplast may be defined as "the total non-living cell wall continuum that surrounds the symplast"[9]. The apoplast comprises the cell-walls, intercellular spaces and xylem vessels and is permeable to aqueous solution. The apoplast can be thought of as the cell wall and the symplasm as the cytoplasm.

Figure 1.2.7 and 1.2.8 represent the symplasm and apoplasm systems and the pathways of transport within them[6].

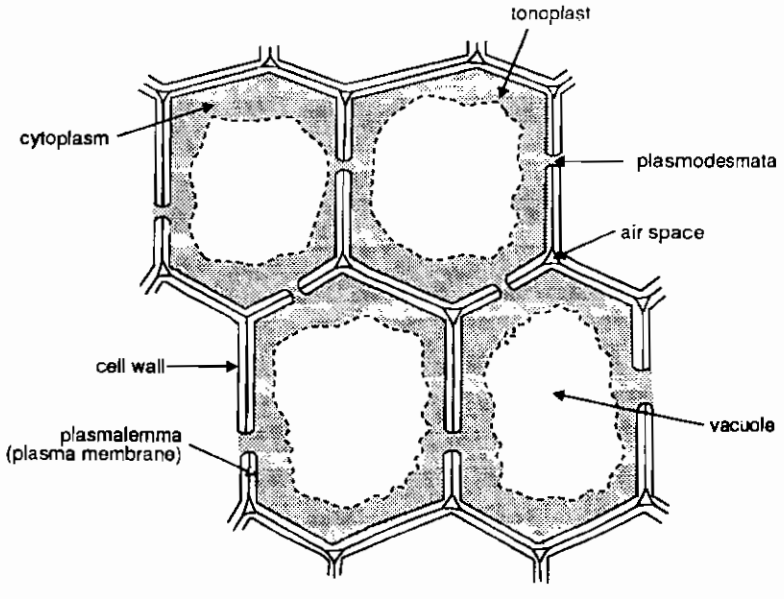


Figure 1.2.7 Schematic representation of the symplasm/apoplasm system. Only one plasmodesma is shown on each wall, the actual number varying from 10-50. The symplasm is stippled, the apoplasm is clear.

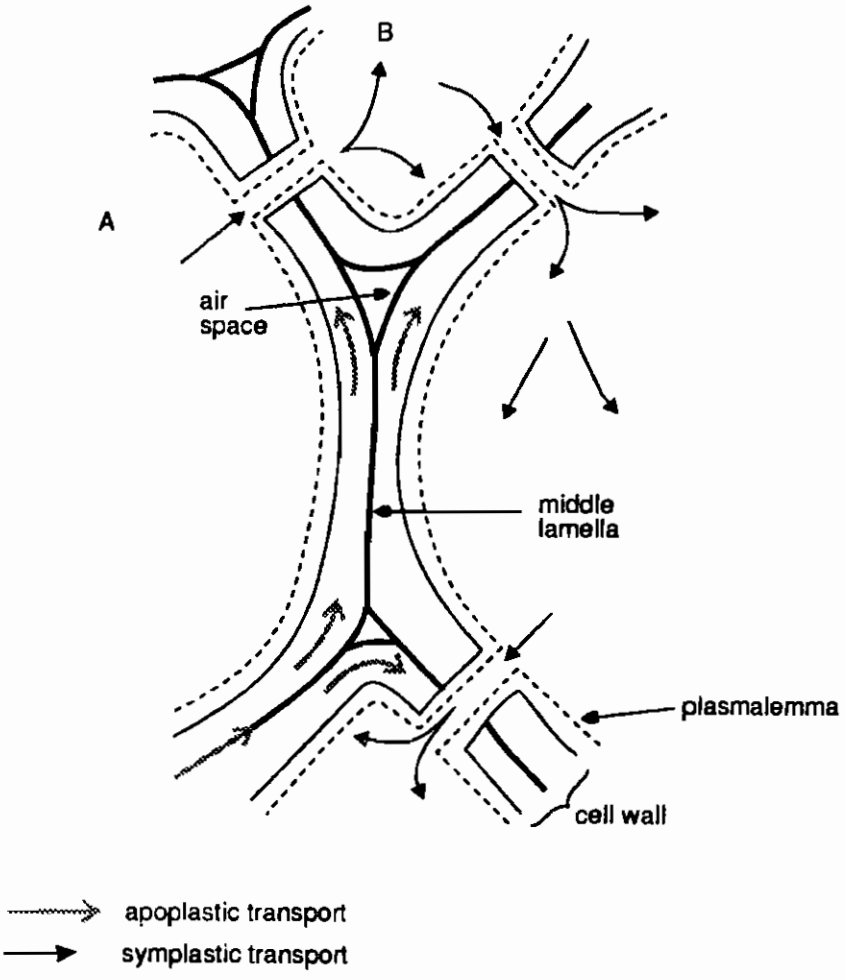


Figure 1.2.8 Apoplastic and symplastic transport in plant tissues. A and B are referred to in the text. Note that movement is not unidirection but can occur in both directions. Light arrows indicate apoplastic transport, dark arrows indicate symplastic transport.

1.2.4 Photosynthesis

Photosynthesis is the process by which plants convert solar energy into chemical energy (which is stored as glucose and oxygen). All the reactions of photosynthesis take place in the organelle known as the chloroplast. The overall equation for photosynthesis can be summarised as

$$6CO_2 + 12H_2O + \text{light energy} + \text{chlorophyll} \rightarrow C_6H_{12}O_6 + 6O_2 + 6H_2O$$

Scheme 1

Photosynthesis takes place in two stages, a light dependent stage called the 'light' reaction, and an enzymatic, light independent stage, called the 'dark' reaction. The terms 'light' and 'dark' reactions can be confusing, for although the 'dark' reactions do not require light, it only requires the chemical products of the 'light' reaction. It is thought that one of the enzymes controlling a step in the dark reaction is indirectly stimulated by light. As a result the terms 'light' and 'dark' reactions are replaced by the terms which more accurately describe the processes occurring during the steps of photosynthesis[10].

In the first stage of photosynthesis- the energy capturing reaction (light reaction), the light energy trapped by the chloroplast is used to form ATP (adenine triphosphate) from ADP (adenine diphosphate) and to reduce electron-carrier molecules.

$$H_2O + NADP^+ + ADP + Pi + \text{light} \rightarrow {}^1/_2\, O_2 + ATP + NADPH + H^+$$

Stage one

Scheme 2

In the second stage of photosynthesis, the chemical products of the first stage are used to reduce carbon from carbon dioxide to a simple sugar (carbohydrate). The incorporation of CO_2 into organic compounds is known as the fixation of carbon.

$$CO_2 + ATP + NADPH \rightarrow (CH_2O) + ADP\ Pi + NADP^+$$

Stage two

Scheme 3

The relationship between stage one (light reactions) and stage two (dark reactions) is represented below (figure1.2.9)[7].

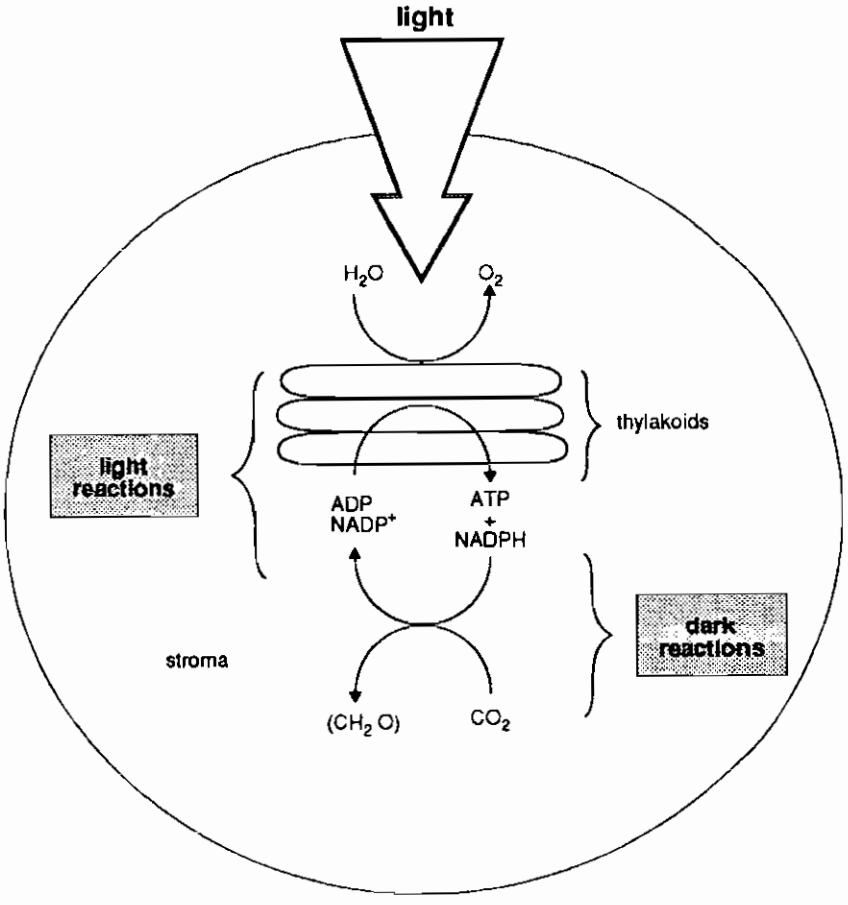


Figure 1.2.9 In the chloroplast ATP and NADPH are formed in the light reaction and CO_2 is reduced in the Dark reaction.

Herbicides that effect photosynthesis do so by inhibiting the energy-capturing reaction. Herbicides do not effect the 'dark reaction'.

The energy-capturing reactions:

There are two photosytems involved in this stage, photosystem I and II. A photosystem is where chlorophyll and other organic compounds are packed in the thylakoids. In photosystem I the reactive chlorophyll *a* molecule is known as P_{700} (P for pigment). In photosystem II the reactive chlorophyll *a* molecule is P_{680}. Photosystem I can operate independently but in general the two systems work together simultaneously and continuously as shown in figure 1.2.10[10].

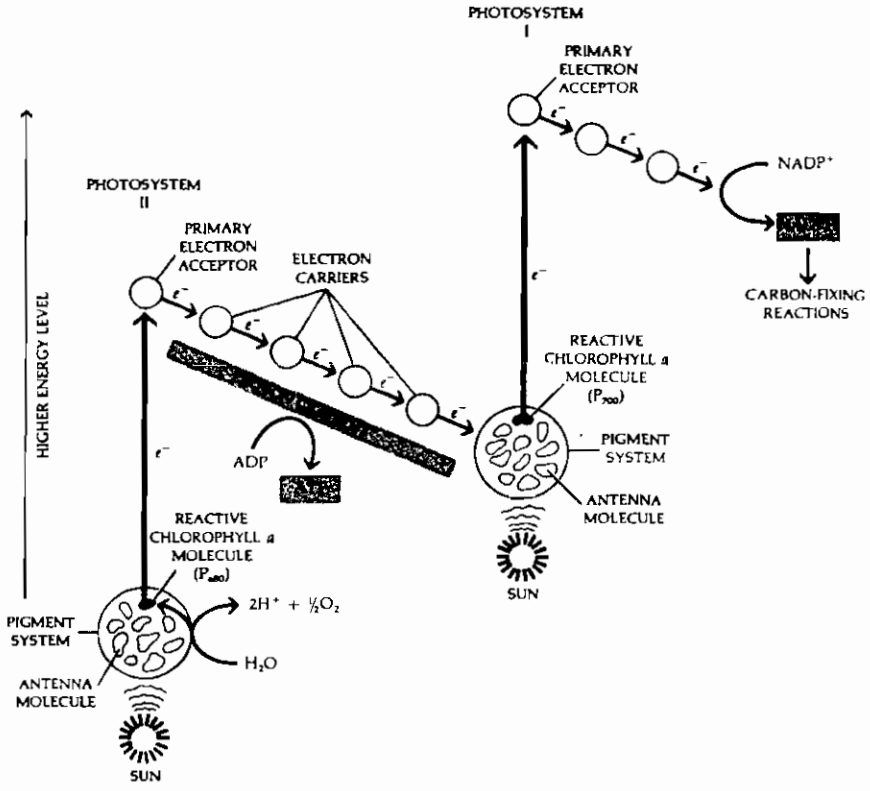


Figure 1.2.10[10] Schematic of photosystem I and II

Light energy enters photosystem II where it is trapped by the reactive chlorophyll *a* molecule P_{680}. An electron from the P_{680} molecule is raised to a higher energy level from which it is captured by an electron-acceptor molecule. The electron then pass along an electron transport chain to photosystem I. As electrons pass along this transport chain, a proton gradient is established. The potential energy of this gradient is used to form ATP from ADP. This process is known as photophosphorylation[10]. Three other events take place simultaneously.

1) The P_{680} chlorophyll molecule, having lost an electron, is seeking a replacement. A water molecule is stripped of an electron and then broken into protons and oxygen gas. The P_{680} molecule accepts this electron.

2) The P_{700} chlorophyll molecule of Photosystem I traps additional light. The P_{700} chlorophyll molecule is oxidised and an electron is boosted to an electron acceptor, from there it moves along an electron transport system to $NADP^+$ as illustrated in figure 1.2.10[10].

3) The electron passed down the electron carriers of photosystem II and replaces the electron removed from the P_{700} molecule of photosystem I.

In the light there is a continuous flow of electrons from water to Photosystem II to Photosystem I to $NADP^+$.

1.2.5 Plant hormones

Strictly speaking plant hormone is an inaccurate term because for a substance to be a hormone it must have the following characteristics;

(1) they must be produced at a specific site,

(2) they must be transported from a separate site of production to a site of action and

(3) they must bring about specific identifiable changes at the site of action.

A number of compounds produced in plants will affect growth, differentiation and certain physiological process, and these compounds have some but not all of the above characteristics of hormones. These compounds then are referred to as plant growth regulators (PGRs). A number of synthetic compounds mimic the effect of naturally occurring PGR and so to avoid confusion the naturally occurring compounds are referred to as hormones and the synthetic compounds referred to as PGRs.

A very important factor concerning a hormone is that its concentration must be controlled to ensure that the rate of the processes, which it effects, is also controlled. The factors involved in this control are illustrated in figure 1.2.11[11].

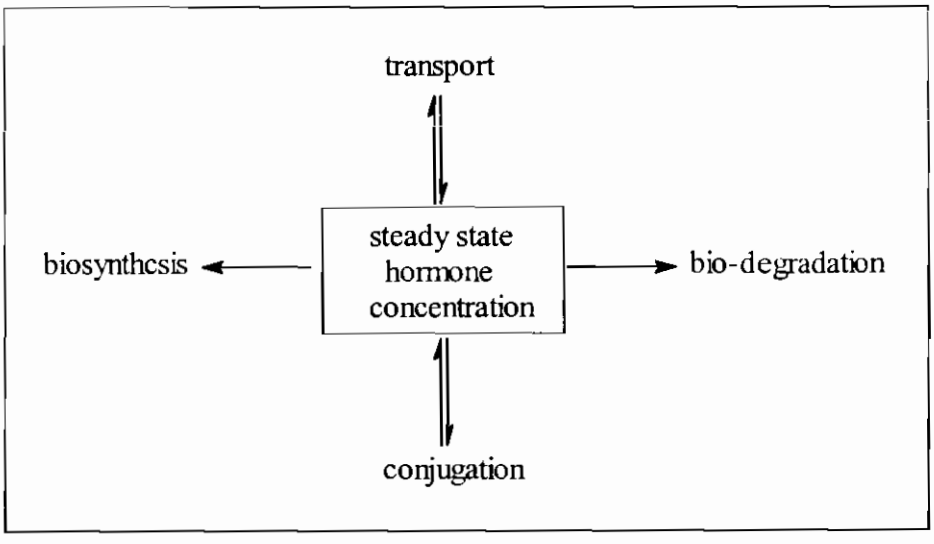


Figure 1.2.11 Factors which influence the steady-state concentration of a hormone

As can be seen from above, the biosynthesis process is irreversible and can only lead to an increase in concentration, whereas the bio-degradation process (also irreversible) can only lead to a reduction. Most plant hormones have been shown to form conjugates with sugars and/or amino acids. The formation of the conjugates

appear to be a detoxifying system for some species as it is irreversible and in others the conjugates act as temporary reversible storage forms.

Plant hormones are grouped into five main classes. These classes partly reflect the order in which they were discovered but also recognise differences in their chemical nature. The five groups are auxins, gibberellins, cytokinins, abscisins and ethylene. Of these five only the auxins are relevant to the herbicide fluroxypyr as it is an auxin-type herbicide.

There are a number of physiological and morphological effects involving auxins.

(i) Cell elongation in stems, coleoptiles and roots.

(ii) Inhibition of growth of axillary buds in apical dominance.

(iii) Formation of lateral roots and adventitious roots.

(iv) Delay of onset of leaf abscission.

(v) Growth of fruit.

(vi) Control of cambial activity.

As mentioned early Auxins were discovered as a result of observations made by Charles Darwin in the 1880's. He noted that if the coleoptile of canary grass was exposed to light from one side, the colcoptile bent towards the light. Experiments carried out showed that a growth-modifying compound was produced in the tip of the coleoptile, then was transported to the subapical zone and there caused cell elongation to occur. These compounds could be collected in an agar block which itself would cause bending when applied asymmetrically to a decapitated coleoptile [11] as illustrated in figure 1.2.12

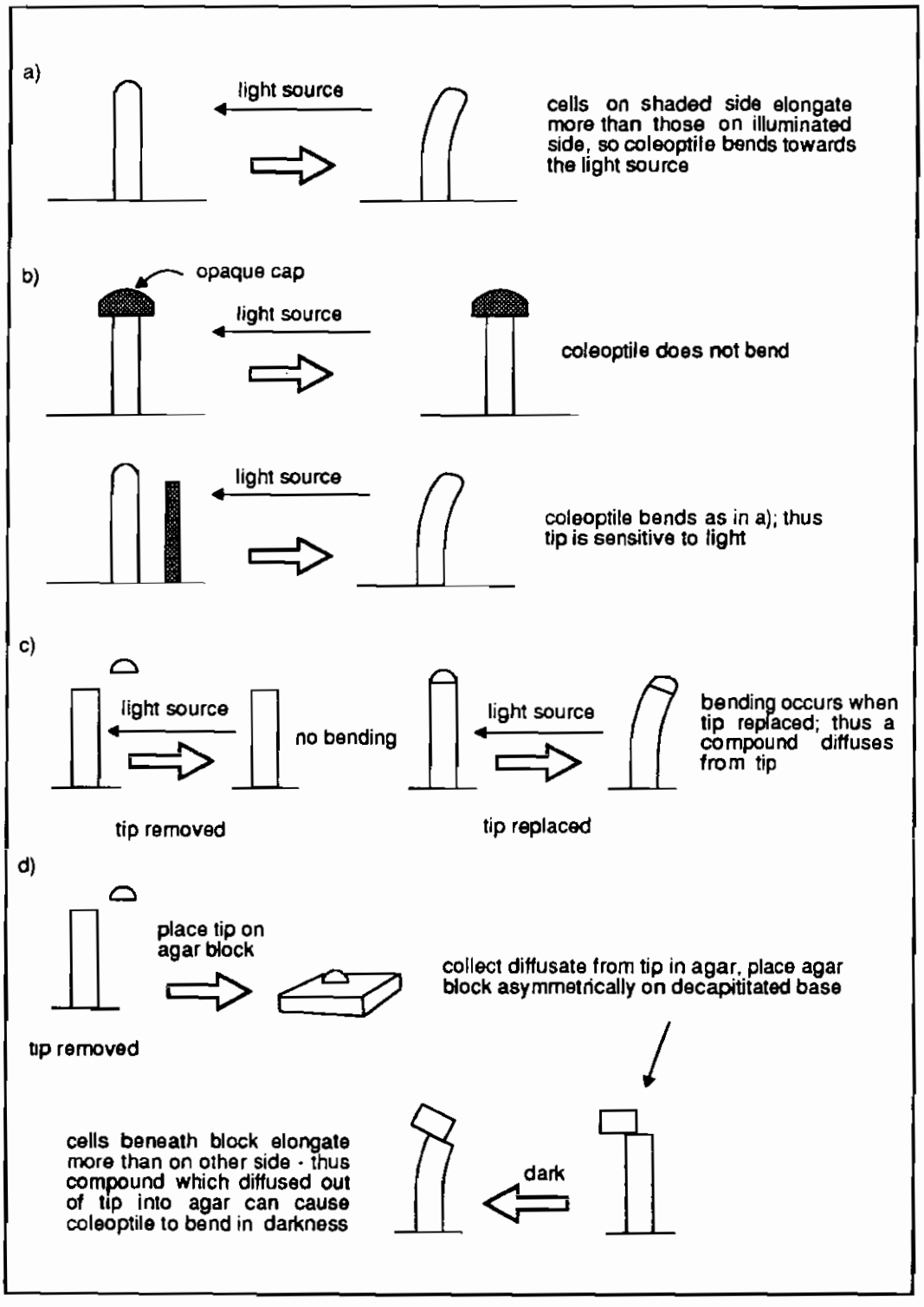
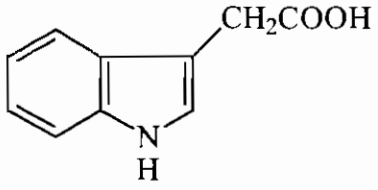
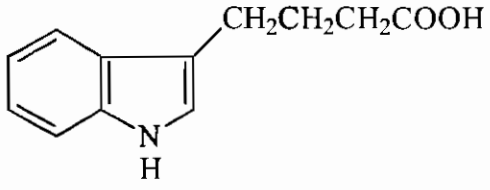


Figure 1.2.12 Experiments which led to the discovery of auxins; a) an intact celeoptile will bend towards the light; b) but only if the tip is exposed to light; c) removal of tip prevents curvature but bending is retained if the tip is replaced; d) an agar block containing a diffusate from an excised tip will cause bending in the dark if placed asymmetrically.

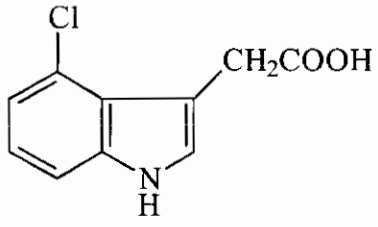
The compound causing the coleoptile to bend was isolated in 1934 by a Dutch scientist Fritz Went and he named it auxin. A compound is said to have auxin activity if it is active in the oat coleoptile test described earlier[11]. Four naturally occurring compounds are known to have auxin activity and are illustrated in figure 1.2.13[11].



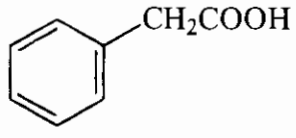
(1) Indole-3-acetic acid (IAA)



(3) Indole-3-butyric acid (IBA)



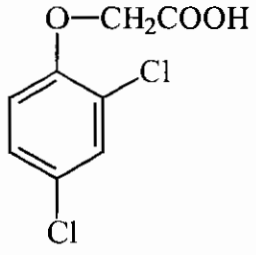
(4) 4-chlorindole-3-acetic acid (4-Cl-IAA)



(5) Phenyl acetic acid (PAA)

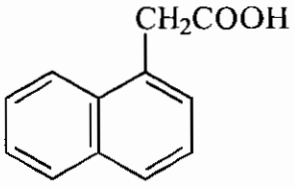
Figure 1.2.13 Structure of natural auxins

IAA is a naturally occurring auxin and is photolabile and is oxidised by IAA oxidase. A large number of compounds are known which are active in auxin bioassays but are stable to bright light and are not degraded by IAA oxidase. These compounds are not naturally occurring and are classed as synthetic auxins as shown in figure 1.2.14.



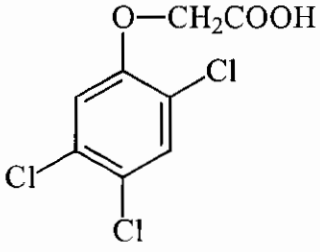
(2)

2,4-dichlorophenoxy acetic acid
(2,4-D)



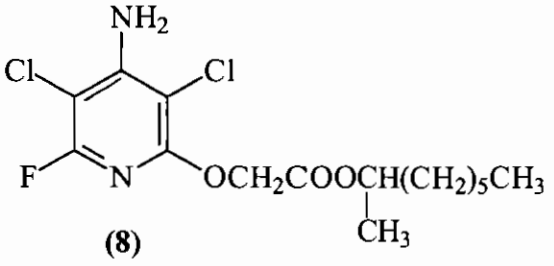
(6)

1-Naphthalene acetic acid
(1-IAA)



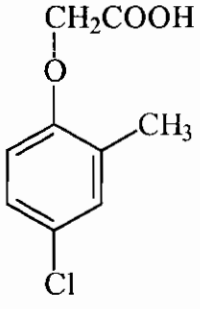
(7)

2,4,5-trichloro phenoxyacetic acid
(2,4,5-T)



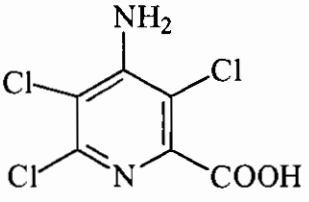
(8)

1-methyl heptyl (4-amino-3,5-dichloro
-6-fluoro-2-pyridinyloxy) acctatc
(fluroxypyr)



(9)

([4-chloro-o-tolyoxy]acetic acid)
(MCPA)



(10)

4-amino-3,5,6-trichloro-pyridine-2-carboxylic acid
(picloram)

Figure 1.2.14 examples of some synthetic auxins[11].

In low concentrations IAA stimulates growth but in high concentrations it inhibits it. At even higher concentrations IAA can be lethal. The concentration of naturally occurring auxins is controlled by the plant. However synthetic-auxins are not governed by these factors. The concentration of auxin needed to kill narrow-leafed plants, such as cereals, is 10 times that needed to kill broad-leaved plants such as poppy. This factor permits the use of some synthetic auxins as selective herbicides.

1.3 Herbicides and there mode of action

1.3.1 Mode of Action

There are over 150 basic compounds that are used as herbicides. They differ in selectivity, absorption, formulation, phototoxicity, translocation, and mode of action, availability and cost. The mode of action can be defined as "the entire sequence of events from the introduction of the herbicide into the environment to the death of the plant"[2]. Another term, which is frequently used, is mechanism of action which refers to the primary biochemical or biophysical lesion leading to death. The exact mode of action of many herbicides is not known. A number of factors effect the mode of action of a herbicide, the absorption and translocation, the molecular fate, biochemical responses, growth and plant structure and selectivity.

Any herbicide may be phototoxic or non-phototoxic to all of the plant species, if it is applied in sufficiently high or low concentrations. For a herbicide to be efficient " it must reach the biochemical or physiologically sensitive site or sites of action in the phototoxic state, at a concentration sufficient to promote severe effects"[3]. Light, temperature and moisture affect the effectiveness of a herbicide. Herbicides once absorbed by the plant, have several molecular fates and can be either metabolised or affect some vital metabolic plant process such as, photosynthesis, amino acid and protein synthesis, pigment synthesis, nucleic acid synthesis (RNA and DNA are essential to information storage and transfer), respiration and energy transfer. One or more vital process must be disrupted in order for a herbicide to kill a weed.

1.3.2 Classification

The classification of herbicides can be based on methods of use, crops to which they are applied, mode of action or chemical structure. One popular method lists the chemicals alphabetically by common name (A1)[12] another lists the chemicals alphabetically by trade names as well as common name (A2)[12]. A second method is to group the compounds chemically (A3)[12]. A third method is by mode of action (A4)[5] and there are some herbicides that remain unclassified using this third method.

1.3.3 Herbicidal selectivity and treatments

Parcelelsus proposition 'Alle Dinge sind Gifte'[3] (all things are poisonous) should be considered when discussing herbicidal selectivity and treatments. If a herbicide is applied in sufficiently high concentration it may act as a non-selective herbicide, but if that same herbicide is used in sufficiently low concentration it may act as a selective herbicide.

A non-selective herbicide is one that doesn't differentiate between one type of plant and another and destroys everything that it comes in contact with. Non-selective herbicides are very useful for total and long-term weed control, for example to keep roads, railways and paths free of plants growth.

A selective herbicide is one which when used causes the death of the unwanted plant (the weed) but doesn't harm the plant of interest (the crop), for example the use of fluroxypyr for the control of broad-leaved plants in cereals.

Selective and non-selective herbicides may be applied through the roots or foliage.

Foliage treatment involves the herbicide being sprayed directly onto the foliage (leaves) of the plant. These herbicides may be contact or translocated (systemic). Contact herbicides effect only the part of thc plant, with which they have come in contact. They are not translocated throughout the plant. Translocated herbicides are ones, which are absorbed by the leaves or roots into the plant and from there translocated (moved) to the active sites.

Soil treatment is when the herbicide is applied to the soil and absorbed through the roots. Once soil applied herbicides reach the roots they must remain long enough in sufficient quantities to be absorbed in effective amounts. If it is a systemic herbicide it must enter the root and be translocated to the active sites. When using a soil applied

herbicide care must be taken to apply the correct herbicide as some herbicides persist for a longer period of time than others.

Herbicides application may be carried out by a number of different methods. Application of a herbicide before the crop emerges, but after it is planted is called pre-emergence herbicide. Application made after the emergence of the crop is called post-emergent herbicides. Sometimes it is advantageous to use the herbicide prior to planting the crop and this is called pre-sowing treatment. Some other types of applications are;

Band: this is where the herbicide is applied in bands over the rows and not over the entire area. This is used when the herbicide is expensive.

Direct: the herbicide is directed towards the ground or weed to minimise contact with the crop.

Overall: the herbicide spray is applied uniformly over the whole area.

Contact pre-emergence: this is where the herbicide is applied to weeds that have developed before the crop emerges.

1.3.4 Herbicide formulations

Herbicides may be applied as liquid sprays or as solid particles. The active herbicide ingredient is normally diluted with a carrier (solvent) or an inert solid material such as clay. The type of carrier to be used is dependent on the mode of action and the treatment of the herbicide. Selectivity of a herbicide may be changed somewhat as a result of the carrier used. Liquid formulations are generally diluted with water. Formulations that are insoluble in water are usually formulated as emulsifable concentrates. An emulsifable concentrate contains the herbicide dissolved in an organic solvent as oil and when diluted with water they form emulsions. The method of formulation to be used depends on the solubility of the active ingredient in the carrier and the mode of action which carries the herbicide from the point of application to the active site, for example, fluoroxypyr is absorbed through the cuticle of the leaf and into the plant cells. Polar herbicides are generally dissolved in polar solvents. Non-polar herbicides are dissolved in non-polar solvents.

Granular formulations for most herbicides are available. Dust formulations are no longer available as they are too liable to drift. Granules are particles made of inert materials such as clay, mixed with the herbicide to provide enough bulk for even distribution[13]. Their effectiveness depends on further wetting to effect dissolution and carry them into the soil. Granular forms may prolong the activity of the herbicide by releasing it slowly into the soil.

Surfactants are frequently added to herbicide formulations to increase their effectiveness. A Surfactant (surface active agent) is a material that exhibits activity at surface or interfaces and is biologically inert. All surfactants lower the surface energy of their solvents. Surfactants may improve or decrease total spray retention, sand influence penetration, surface tension and drop size. They may act as solubilising agents and aid in the redistribution of the herbicide upon rewetting. The shelf life of a herbicide may be lengthened by the addition of other additives which stabilise the formulation and prevent degradation to unwanted products.

1.3.5 Mixture of herbicides

One of the most effective ways to increase the numbers of weed species killed selectively in a crop is to mix appropriate herbicides. The herbicides must be compatible that is there must be no undesirable changes in their physical properties as a

result of mixing. The interaction between the herbicides must be beneficial and particular mixtures are usually selected because of the individual properties of each herbicide. The advantage of using mixtures of herbicides is that it broadens the spectrum of weed control and sometimes the dosage of any one herbicide can be reduced.

1.3.6 Absorption and translocation

After a herbicide is applied to a plant it must then be absorbed and translocated. The chemical and physical properties of a herbicide influence the rate and pathway of absorption and translocation. The absorption of herbicides is influenced by environmental factors such as humidity, temperature and light. The site of application also has an important bearing on the absorption and translocation of herbicides. The physicochemical properties of herbicides that are applied to foliage are very different to those that are applied through the soil. It must be remembered that the upper part of the plant is hydrophobic where the leaves and stem are covered by a waxy cuticle. The lower part is hydrophilic and the main function of the roots is to take in water and water soluble substances.

1.3.7 Foliar applied herbicides

The activity of foliar applied translocated herbicides depends largely on factors that govern the amount of active ingredients reaching the active site. The efficiency of cuticle retention and penetration, absorption from symplast, short- and long- distance transport, metabolism and the degree of immobilisation at metabolically non-active sites may determine activity and selectivity as illustrated in figure 1.3.1[14]. Penetration, retention and absorption largely influence the activity of contact herbicides.

Absorption through the leaves occurs either via the cuticle or the stomata. Besides absorption of the herbicide by the leaf a number of other events may occur.

(1) It may evaporate into the environment.

(2) The carrier solvent may evaporate leaving behind the crystalline form.

(3) It may penetrate into the cuticle and remain there in solution.

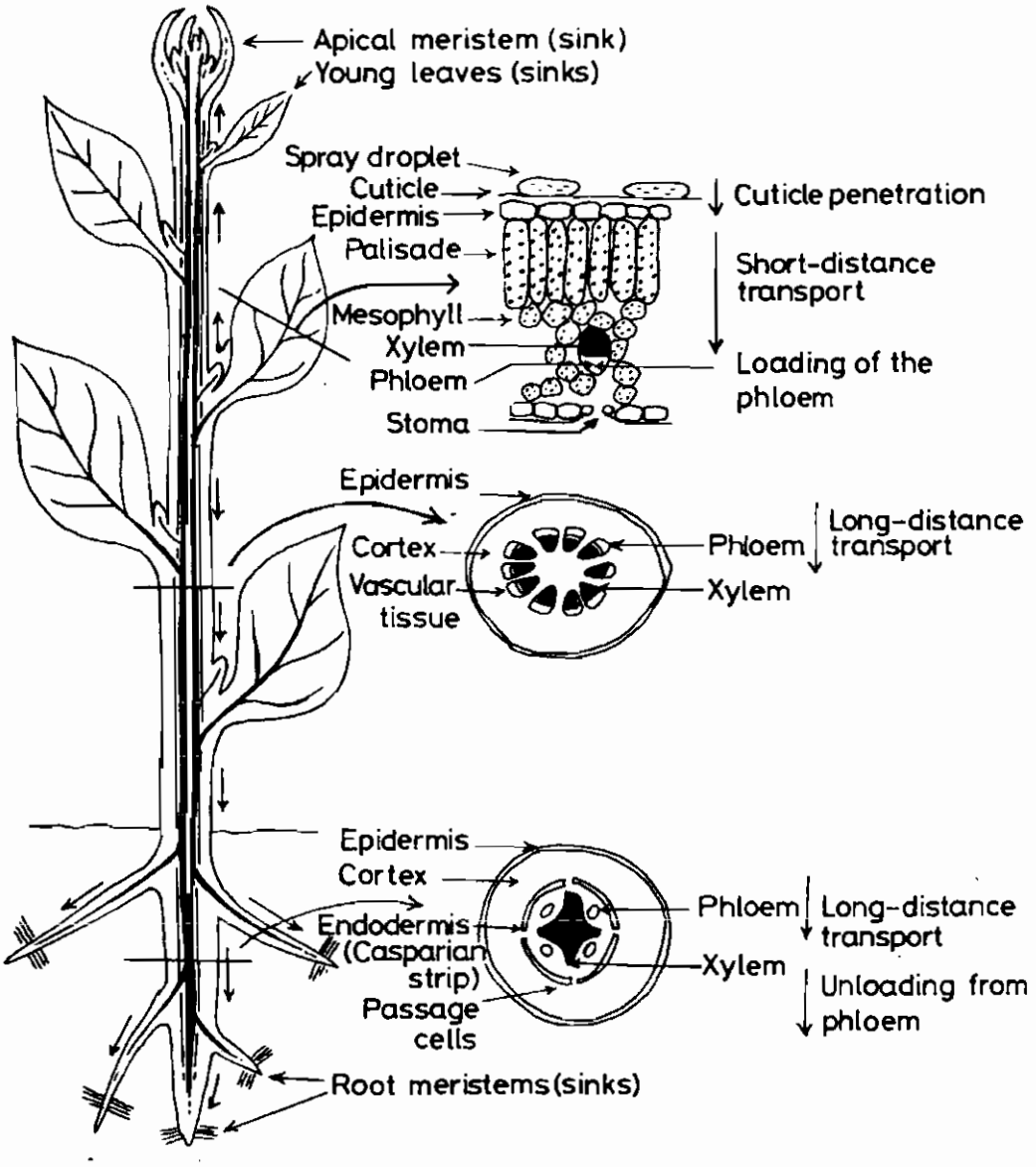


Figure 1.3.1 A schematic view of the probable stages and route of uptake and translocation of a foliage-applied systemic herbicide.

Stomatal absorption is not thought to be of major importance as the stomata are positioned on the underside of the leaf, which makes penetration difficult. Penetration of the stomata can be obtained if the surface tension of the solution is equal to or less than the critical surface tension of the plant surface, that is, if the droplet forms zero contact angle on the surface[14]. Very low surface tension is difficult to achieve, making stomatal absorption less important and absorption is primarily via the cuticle.

Cuticle absorption is thought to occur via two routes:

(1) through the epicuticular wax or

(2) through the cutin as illustrated in Figure 1.3.2 [15].

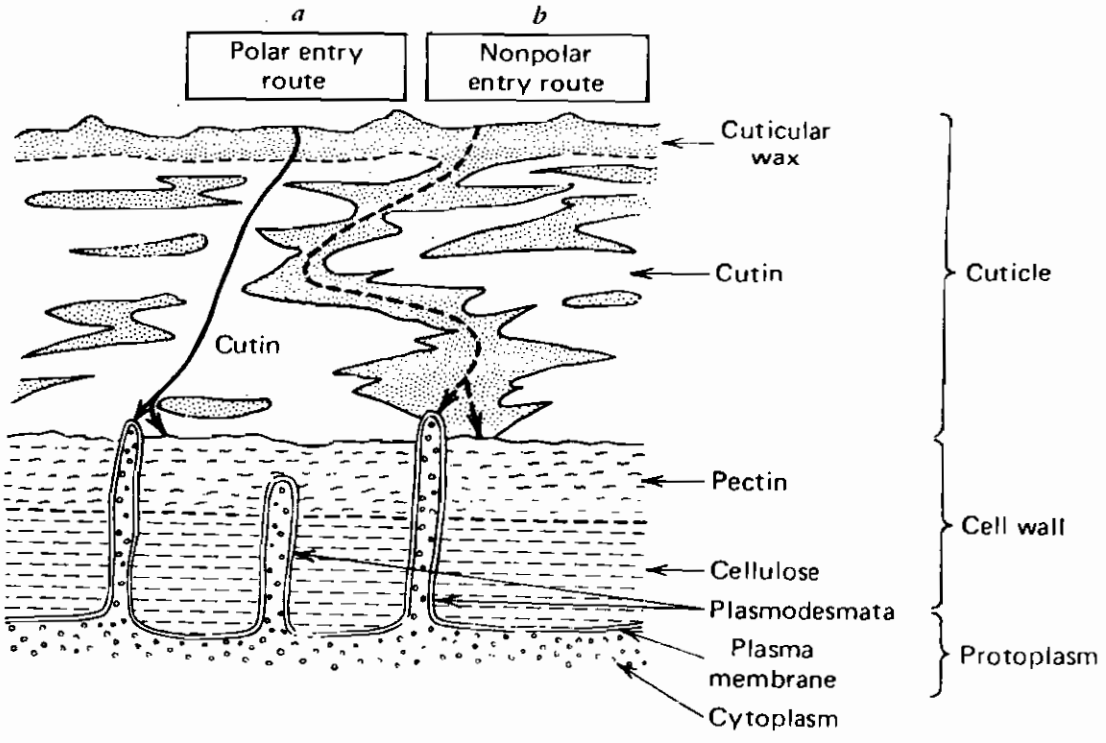


Figure1.3.2 Hypothetical diagram representing the foliar absorption aspects of cuticle-cell wall-protoplasm structure. Hypothetical routes of entry of a) polar and b) nonpolar herbicides.

The epicuticular waxes of most plants contain complex mixtures of long chain alkanes, primary and secondary alcohols, ketones, aldehydes, fatty and hydroxy fatty acids and esters. Cutin is composed of crosslinked fatty acid polymers and has hydrophilic characteristics due to –OH and –COOH groups. It also has lipophilic properties due to $-CH_2$ and $-CH_3$ groups[16]. Non-polar herbicides are absorbed through the cuticular wax and polar herbicides are absorbed though the cutin as shown in figure I.3.2. Penetration through the cuticle seems to involve four major steps,

(1) sorption into the cuticle

(2) movemcnt across the cuticular

(3) desorption into the apoplast

(4) uptake by the underlying cells.

Penetration of the cuticle is believed to be a physical process, which may be directly, affected by factors such as; pH, herbicide concentration, surface tension, leaf age, molecular structure, additives and environmental factors. Polarity of an applied herbicide appears to be a critical factor and non-polar compounds are more readily sorbed than polar compounds. Fluroxypyr methylheptyl ester **(8)** and 2,4-D **(2)** are more readily sorbed as undissociated molecules.

1.3.8 Soil applied herbicides

Soil applied herbicides are absorbed via roots, emerging shoots and subterranean organs. The absorption and translocation within the root is not fully understood. A soil-applied herbicide must first pass through the cuticle of the root. The cuticles of roots appear to be more permeable to herbicides than the cuticles of leaves. The herbicide must penetrate the cell walls and the plasmalemma. In addition the herbicide must pass through the casparian strip to reach the xylem and phloem. The absorption of the herbicide by the roots proceeds via three routes, apoplast, symplast and apoplast-symplast are illustrated in figure 1.3.3[15].

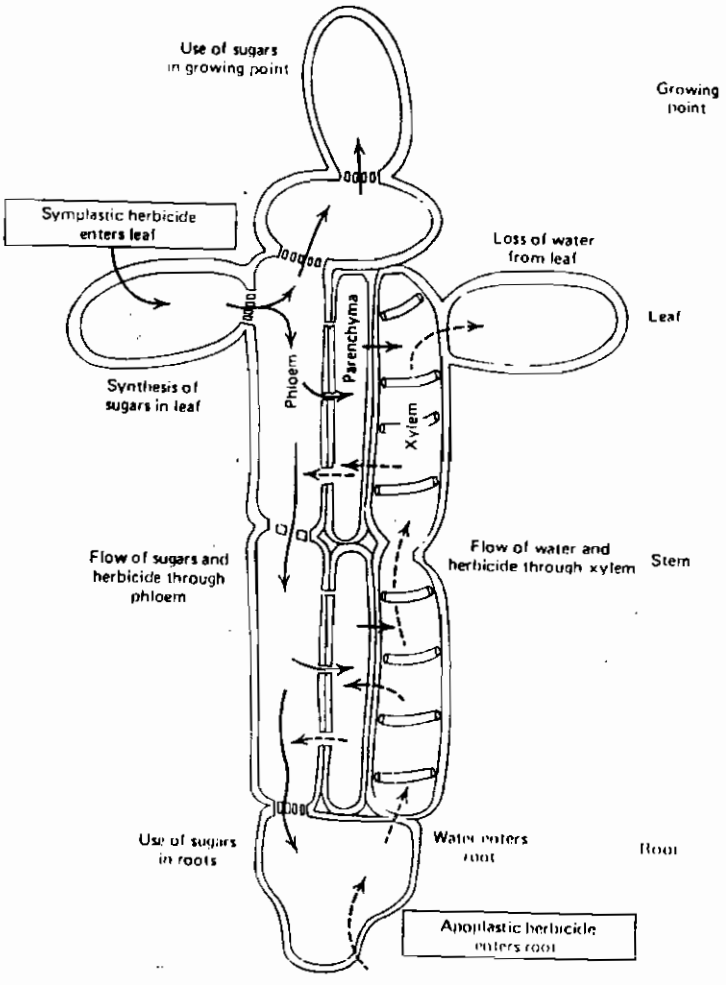


Figure1.3.3 Diagram representing routes of translocation of herbicides in plants.

If the herbicide is absorbed into the apoplast system it moves into the xylem through the cell walls and casparian strip. If absorbed symplastically the herbicide initially enters into the cell walls and into the protoplasm of the cells of the epidermis. From the protoplasm the herbicide passes sequentially into the endodermis, stele* and phloem via the plasmodesmata. The apoplast-symplast route is when the herbicide enters symplastically and once past the casparian strip re-enters the apoplast and then enters the xylem. In soil-applied herbicides after absorption by the roots entry into the xylem is more important than entry into the phloem as there is rapid translocation

* A stele is the cylindrical central portion of the axis of a vascular plant, including pith, xylem and phloem surrounded by a pericycle.

upwards from the roots in the xylem (transpiration stream) under most conditions, but only limited upward transport in the phloem.

1.3.9 Translocation through the plant

Once the herbicide has been completely absorbed, the translocation of the herbicide to the site of action must take place for the herbicide to have the desired effect. Herbicides are translocated within the plant through the symplastic and apoplastic systems. All herbicides enter both systems to a limited degree. Certain herbicides can move readily from one system to the other (phloem ↔ xylem) during transport.

Apoplasticly mobile herbicides, which are absorbed by the roots enter the xylem and are swept upwards with water in the transpiration stream. The driving force for this movement is the removal of water from the leaf by transpiration. When apoplasticly mobile herbicides are absorbed by the leaves, they remain in the treated leaves, they are not translocated through the plant. Under conditions that permit the reversal of the transpiration stream that is very high humidity and very dry soil the herbicide will be translocated.

Symplasticaly mobile herbicides for example fluroxypyr, which are absorbed by the leaves move along with the products of photosynthesis in the phloem. The mechanism and driving force for phloem transport is not certain but the most widely accepted theory is that of mass flow proposed by Munch (1930)[15]. Transport of the herbicide is along a physical turgor or osmotic gradient in the phloem and is maintained by a source-sink relationship. A source is any structure where photosynthesis is occurring for example in the leaves. A sink is any structure that requires sugar for growth, for example the roots and developing leaves. High concentration of sugar in the phloem causes water to move into the phloem by osmosis and the high turgor pressure then forces the contents of the sieve tubes of the phloem to flow to areas of low turgor pressure (sink). For this to occur the osmotic pressure or concentration of sugar contents of the phloem at the source must be greater than that of the surrounding cells. This movement of sugar against a concentration gradient requires energy.

The pathway of phloem-mobile herbicides follows the source sink relationship of the photosynthate. When symplasticly mobile herbicides enter the roots they may accumulate in the root tips and other nearby sinks, but little if any is translocated to the shoots.

1.3.10 Biochemical Responses

After the absorption and translocation of a herbicide it can undergo a series of biochemical changes. The degradation of herbicides by plants is an important mechanism of detoxification generally minimising the possibility of transmission of the compound through the food chain.

Herbicide degradation in higher plants may result from a wide range of chemical reactions, which include oxidation, decarboxylation, deamination, dehalogenation, dethioation, dealkylation, dealklyoxylation, hydrolysis, hydroxylation and conjugation mechanisms. Most of these reactions are catalysed by specific enzymes though some are non-enzymatic in nature. Usually when herbicides are metabolised in the plant a less toxic compound is produced but occasionally a more toxic compound results. The ability of a plant to degrade a herbicide dictates whether the plant is tolerant or not to that particular herbicide. If the plant metabolises the herbicide before it reaches the active site then it is deemed tolerant to that particular herbicide.

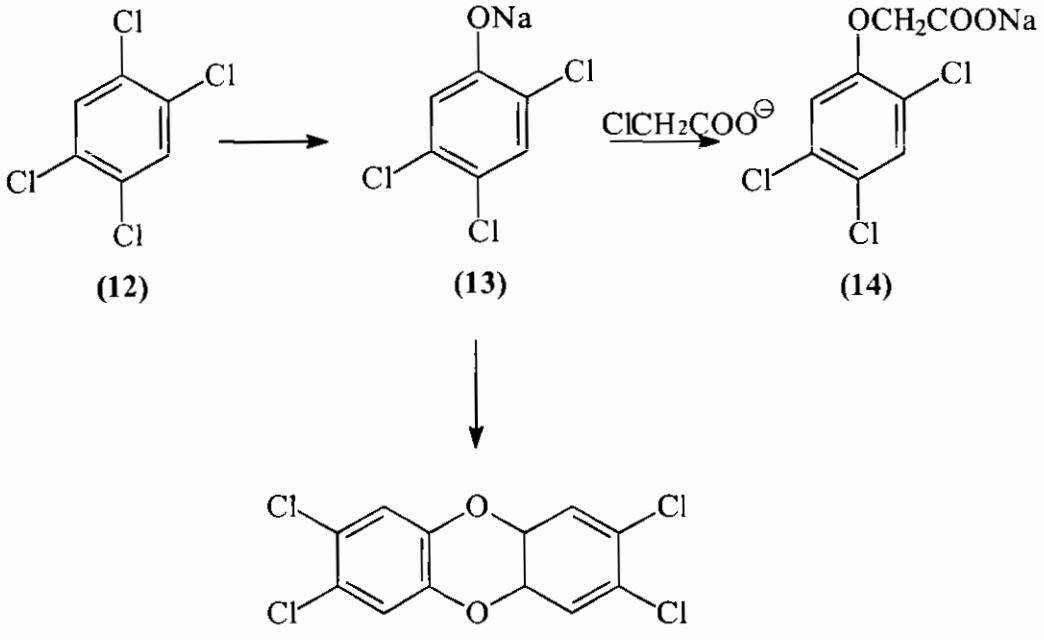
1.3.11 Growth regulator-type (synthetic auxin) herbicides

The growth regulator-type herbicides are the oldest class of synthetic organic herbicides. Synthetic auxins can be classified into four herbicidal families (as shown in figure 1.3.4). These families are benzoic acids, the phenoxy carboxylic acids, the pyridine carboxylic acids and the quinoline carboxylic acids. A new family called the semicarbaones is being developed by BASF[17].

Herbicide	Company	Trade Names
Benzoic acids		
Dicamba	BASF, Novartis	Banvel, Clarity,
Phenoxy Carboxylic acids		
2,4-D	Rhone-Poulenc, others	Weedar, Weedone, others
2,4-DB	Rhone-Poulenc, others	Butyrac, Butoxone, others
Dichlorprop	BASF, Rhone-Poulenc,	Many
Dichloroprop-P	BASF	Duplosan DP
MCPA	Rhone-Poulenc, others	Many
MCPA-thioethyl (also phenothiol)	Hokko	Herbit
MCPB	Rhone-Poulenc, others	Many
Mecoprop	AgrEvo, others	Many
Pyridine carboxylic acids		
Clopyralid	Dow AgroScience	Lontrel, stinger, Reclaim, Hornet, Stinger III.
Fluroxypyr	Dow AgroScience	Starane
Picloram	Dow AgroScience	Tordon
Triclopyr	Dow AgroScience, others	Garlon, Remedy, others.
Quinoline Carboxylic acids		
Quinclorac	BASF, others	Facet, others
Quinmerac	BASF	Fiesta, others
Semicarbazones (Polar Auxin Transport Inhibitor)		
Diflufenzopyr*	BASF	Distinct
*Experimental product		

Figure 1.3.4 Synthetic auxin herbicide families.

The first growth regulator herbicides were the phenoxy carboxylic acids for example 2,4-D (**2**), MPCA (**9**) and 2,4,5-T (**7**) (as shown in Figure 1.2.15), which were introduced at the end of World War II, following the publication of wartime research on their growth regulating and herbicide activities[18,19]. These herbicides quickly revolutionised weed control. 2,4-D (**2**) and MCPA (**9**) are used for the control of broad-leaved weeds in small grains, corn and grass pastures and 2,4,5-T (**7**) was used extensensively as a brush and forestry herbicide. The phenoxy herbicides may be applied to leaves, stems or by way of the soil (roots of plants). 2,4,5-T (**7**) was also one of the components of 'Agent Orange', which was used by the United States to defoliate jungle area's during the Vietnam war. The production of 2,4,5-T (**7**) was stopped in the 1980's because of a contaminant (dioxin) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) **(11).** This contaminant was produced during the manufacture of 2,4,5-T during the high-temperature hydrolytic conversion of 1,2,4,5-tetrachlorobenzene (**12**) to 2,4,5-trichlorophenol (**13**) and this impurity could not be removed see figure 1.3.5.



(12) **(13)** **(14)**

(11)

Figure 1.3.5

Dicamba (**15**) figure 1.3.6 belongs to the benzoic acids group and was first introduced in 1965 by the Velsicol Chemical Corporation. It was used for both pre-emergence and post emergence weed control in maize and post emergence weed control in small grains.

The Dow chemical company has introduced a number of pyridine carboxylic acid herbicides. These are foliar applied, selective growth regulatory herbicides. An example is Picloram (4-amino-3, 5,6-trichloro-pyridine-2-carboxylic acid) **(10)** which was introduced as Tordon in 1963 for the control of annual weeds and deep-rooted prennnials and is mobile in soil and very persistent. Tordon can often be detected up to 2 years after application and as a result its use is restricted. Triclopyr (3,5,6-trichloro-2-pyrinyloxyacetic acid) **(16)** figure 1.3.6 was marketed as Garlon in 1970 and may be used for the control of certain 2,4-D resistant weeds in cereals and for the control of unwanted brush and perennial weeds in industrial areas. It is highly active against woody plants including Ash, which is normally difficult to control. Triclopyr **(16)** has an average half-life of 46 days.

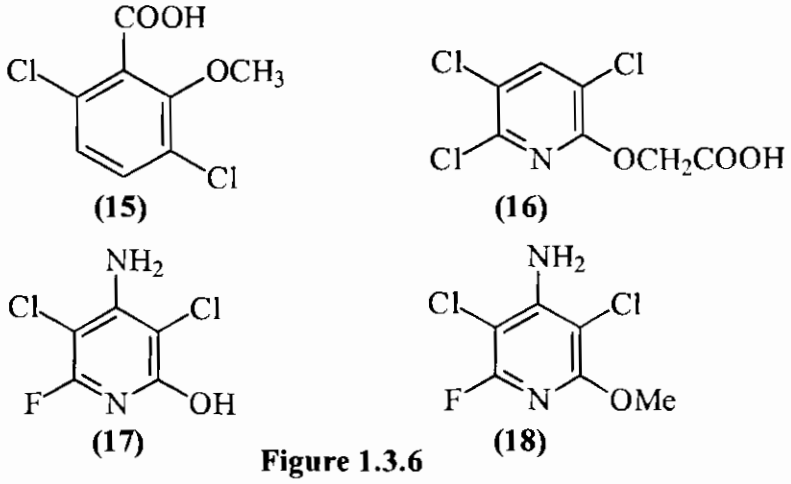
Another pyridine carboxylic acid herbicide is fluroxypyr **(8)**. It was first prepared in 1985 by Dow Elanco and is marketed as Starane[20]. It is used for the control of annual broad-leafed weeds in cereals and perennial ryegrass. The high level of control of *galium aparine* gives it a distinct advantage over many other herbicides. Until 1998 fluroxypyr was only marketed in Europe as a herbicide. However United Ag Products (Platte Chemical Company) are now developing it for use in small grains and corn in the US. It is thought that UAP is moving towards a national registration, as fluroxypyr is effective on *Kochia* biotypes that are resistant to other herbicides as well as on catchweed bedstraw, speedweeds and volunteer potatoes. Fluroxypyr is an off white crystalline solid with a melting point of 57.5-58°C and is nearly insoluble in water 0.09mg/L.

The mode of action of the phenoxy carboxylic acids has been the subject of a vast amount of research since their discovery. However the biochemistry of their toxicity and the reasons for their selectivity is not completely understood. It is thought that the phenoxy carboxylic acids cross the cuticle readily by diffusion down a concentration gradient either using the lipophilic route or the hydrophilic route. Foliar applied phenoxy herbicides characteristically move from the leaves, by way of the symplast that is they are translocated by the phloem, however some translocation in the xylem may occur.

Fluroxypyr is applied as fluroxypyr 1-methylheptyl ester. After predominantly foliar uptake, the ester is rapidly hydrolysed to the parent acid (half-life 2-5hours), which is the herbicidally active form and translocated rapidly via the phloem to other

parts of the plant[21]. Herbicide penetration and translocation was determined after experiments using ^{14}C-pyridine-ring labelled fluroxypyr. This was applied to leaves of susceptible species such as *stellaria media* and *Galium aparine*[22]. Susceptible species developed symptoms typically associated with auxin-type herbicides, for example epinasty and growth aberration. Fluroxypyr is degraded microbiologically (half-life 1-3 weeks) into two primary metabolites 4-amino-3,5-dichloro-6-fluoropyrindin-2-ol **(17)** and 4-amino-3,5-dichloro-6-fluoro-2-methoxy pyridine **(18)** figure 1.3.6, then to other secondary metabolites and finally to carbon dioxide and water[23,24]. The biochemical effects of auxin-type herbicides are varied and many of these are secondary in nature. The actions of auxin type herbicides appear to be similar to that of the natural auxin IAA **(1)**. However as mentioned earlier IAA **(1)** is under metabolic control, which results in normal growth, whereas the level of these herbicides is not controlled. This results in abnormal growth in plants treated with these herbicides. Nucleic acid and protein synthesis seem to be important sites of action, also there is evidence that these compounds act as uncouplers and inhibitors of oxidative phosphosphorylation.

To summaries the mechanism of pesticidal action for fluroxypyr is that it induces auxin-type responses in susceptible annual and perennial broadleaf weeds. Once absorbed into the plant, it accumulates in growing tissue (sinks) to higher concentrations than the native auxin does, and degrades more slowly. Plant growth is disrupted by the deregulation of cellular growth process following binding of fluroxypyr to plant auxin receptor sites. Fluroxypyr also interferes with the plants ability to metabolise nitrogen and produce enzymes. When a plant's strict growth regulation is disrupted in this fashion, plant growth becomes disorganised, disrupting key metabolic process and results in plant death.



(15) **(16)** **(17)** **(18)**

Figure 1.3.6

1.4 Chemistry of pyridines

1.4.1 General introduction

Organic compounds have an enormous diversity of structure and many of these structures contain ring systems. If the ring system is made up of atoms of carbon and at least one other element, the compound is classed as heterocyclic. The elements that commonly occur with carbon in the ring are nitrogen, oxygen and sulphur. Heterocyclic compounds can be aliphatic or aromatic and have a wide range of applications as pharmaceuticals, agrochemicals and veterinary products. Heterocyclic compounds are widely distributed in nature and many are of fundamental importance to living systems. The genetic material DNA contains heterocycles and many useful alkaloids such as the anaesthetic cocaine **(19)**, the narcotic nicotine **(20)** and the antimalarial quinine **(21)** all contain heterocyclic ring systems as do the herbicides, paraquat **(22)** and fluroxypyr **(8)**, (figure 1.4.1).

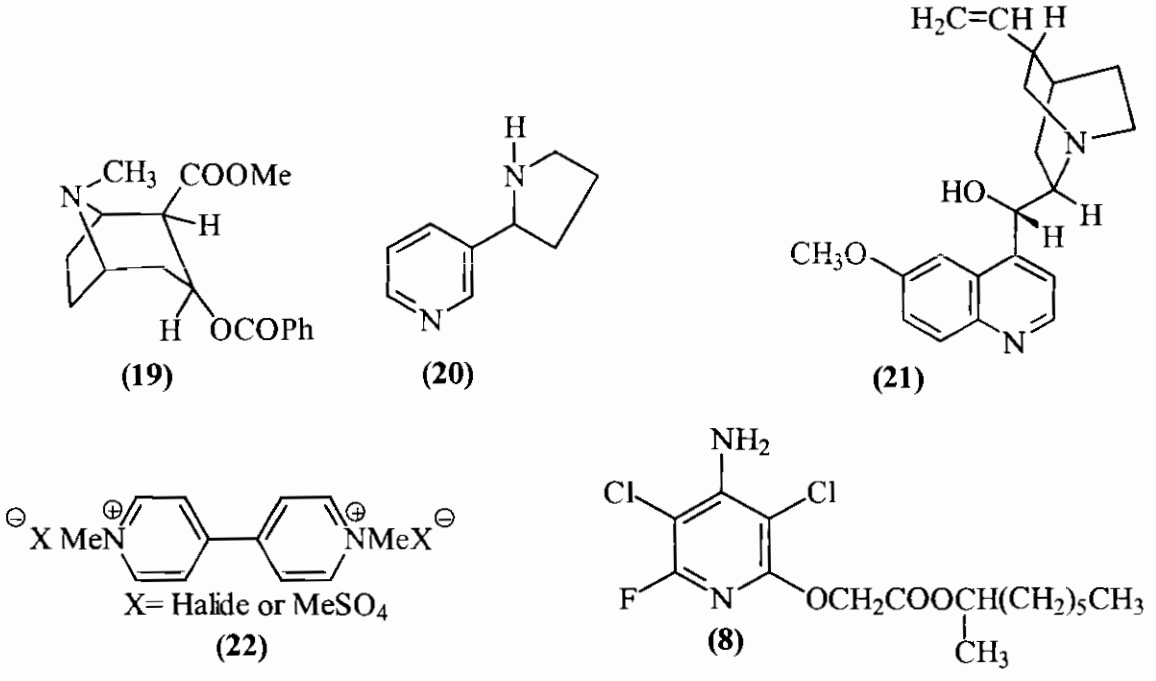


Figure 1.4.1

In addition the antibiotics penicillin **(23)** and a variety of vitamins such as riboflavin **(24)**, pyridoxol (vitamin B_6) **(25)** and ascorbic acid **(26)** are also heterocyclic compounds, (figure 1.4.2.)

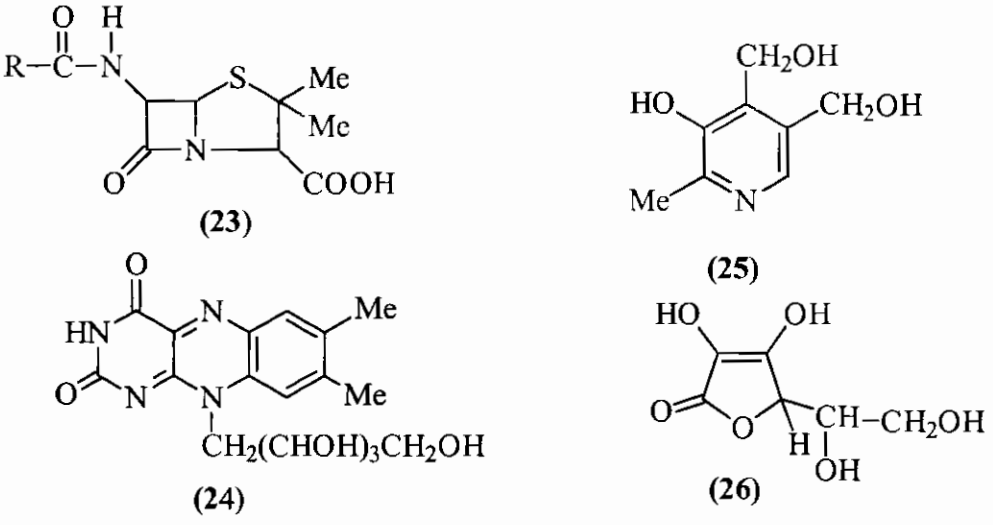


Figure 1.4.2

There is an important group of heterocycles with structures analogous to that of benzene but with a heteroatom replacing one or more of the carbon atoms of the benzene ring. Pyridine **(27)** (azabenzene), with one ring nitrogen atom is the best known of such compounds. Like benzene, pyridine **(27)** is planar, the ring system being a slightly distorted hexagon because the C-N bonds are shorter than the C-C bonds. It can be represented by a cyclic structure made up of 5 sp_2 hybridised carbon atoms, to each of which is attached a hydrogen atom and one sp_2 hybridised nitrogen atom as shown in figure 1.4.3. Each of the six atoms of the ring has a p-orbital orthogonal to the plane of the ring. This structure is similar to that of benzene in having a complete cycle of p-orbitals containing six electrons, but differs in having a lone pair of electrons in the plane of the ring.

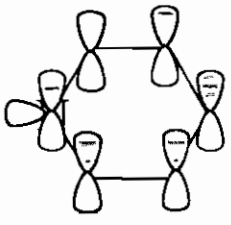
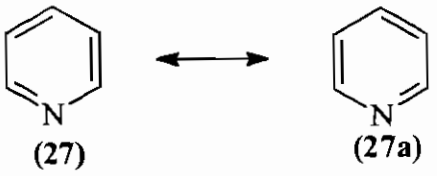


Figure 1.4.3

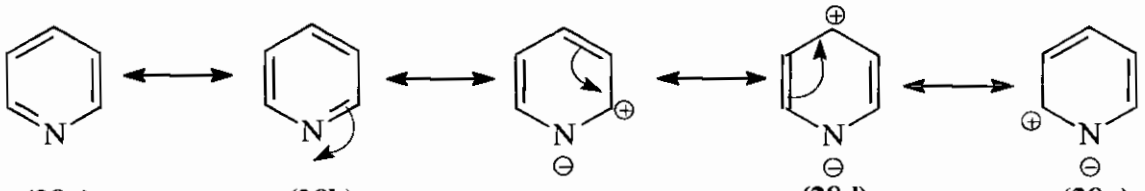
Pyridine **(27)** is conveniently represented by one of two equivalent Kekule structures as shown in Scheme 4



(27) **(27a)**

Scheme 4

Pyridine **(27)** has bond lengths intermediate between normal double and single bond length (C-C = 1.39 Å and C-N = 1.34 Å) as might be expected of an aromatic compound. Introduction of heteratoms to the benzene structure allows for more canonical forms in the resonance hybrid and the electronegativity of the heteroatom localises negative charge. In pyridine **(27)**, canonical forms **28a to 28e,** Scheme 5 are possible and so positions 2, 4 and 6 in the ring have a partial positive charge. The effect of the heteroatom is very similar to the effect of an electron withdrawing substituent at that position on a benzene ring.



(28a) **(28b)** **(28c)** **(28d)** **(28e)**

Scheme 5

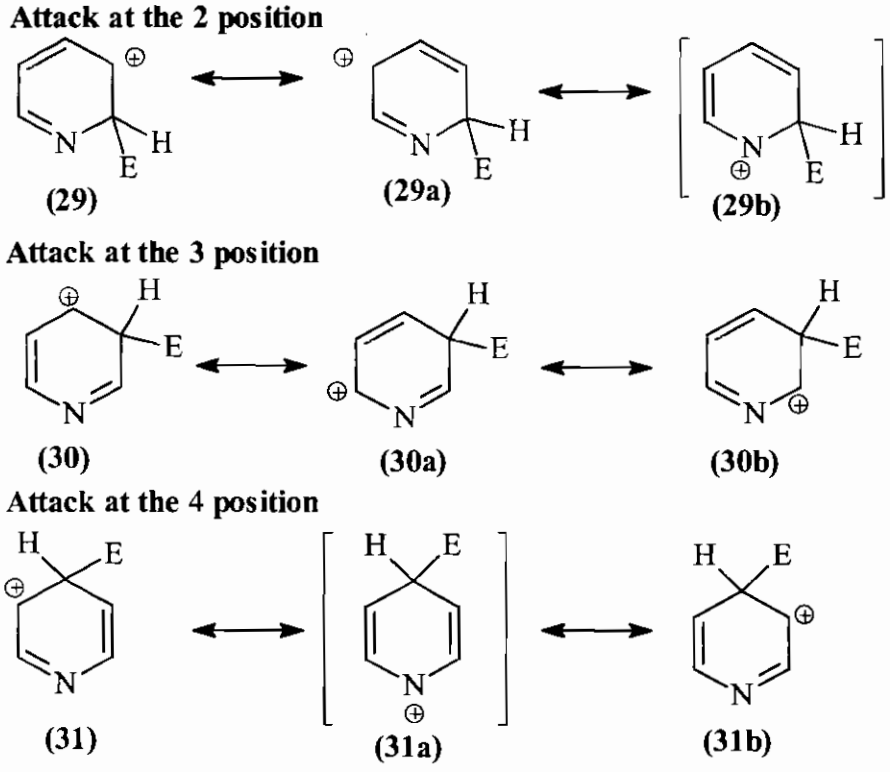
1.4.2 Reactions and Reactivity

Pyridines as tertiary amines:

Pyridine **(27)** and its simple derivatives are weak bases. Pyridine **(27)** itself has a pK_a 5.23 at 20°C. Electronwithdrawing substituents in the ring at the 2 and 6 positions lower the basity of pyridinc and the starting material pentachloropyridine has a pK_a – 6.02. As tertiary bases pyridines undergo protonation by acids, quaternisation with alkylating and acylating agents and N-oxidation by peracids. The more weakly basic pyridines require stronger oxidising agents or reaction conditions, pentachloropyridine for example is oxidised by peroxytrifluoroaetic acid[25] or hydrogen peroxide and an organic acid in the presence of sulphuric acid[26].

Pyridine as benzene analogues:

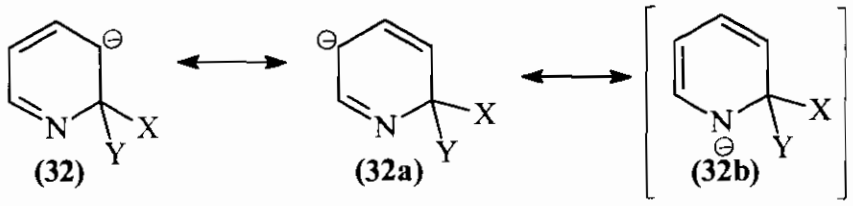
The electrophilic substitution of pyridine **(27)** and its simple derivatives may be accomplished only with extreme difficulty. The attack of the electrophile on carbon is selective, it tends to go mainly at the 3- and 5- position which have the greatest π-electron density. The intermediates produced by electrophilic attack at these positions are the least destabilised by the presence of the nitrogen atom. The resonance structures in Scheme 6, show the destabilising influence of the nitrogen atom on the intermediates produced by eletrophilic attack at the 2, 4 and 6 position. The intermediates 29b and 31a with the positive charge on the nitrogen are unstable and don't contribute to the overall stability of substitution in the 2 and 4 position thus there are only two real resonance structures. With substitution at the 3 position no such unstable intermediates occurs and consequently substitution at the 3 position predominates.



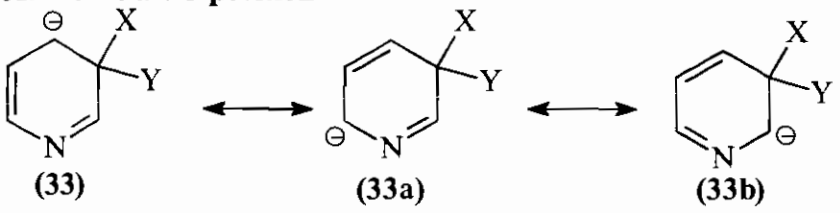
Scheme 6 Intermediates in the electrophilic substitution of pyridine

Nucleophilic substitution is difficult in unsubstitituted benzenes but it is much easier in pyridines particularly at the 2 and 4 positions which are activated to nucleopilic substitution by the electron withdrawing nitrogen atom. Nucleophilic displacement occurs most readily at the 2 and 4 positions. The intermediates in such processes are shown in Scheme 7. Structures for anions in which the negative charge can be delocalised on to nitrogen are stabilised relative to the others. Intermediates 32b and 34a are stabilised so that 2 and 4 substitution is facilitated over 3 substitution.

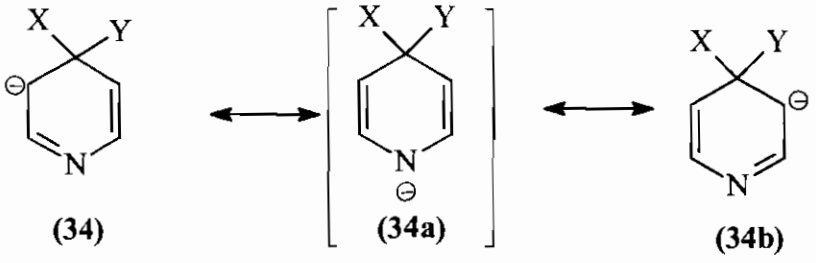
Attack at the 2 position



Attack at the 3 position

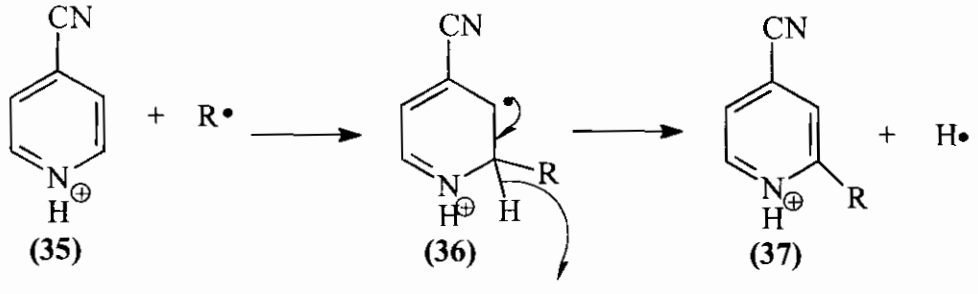


Attack at the 4 position



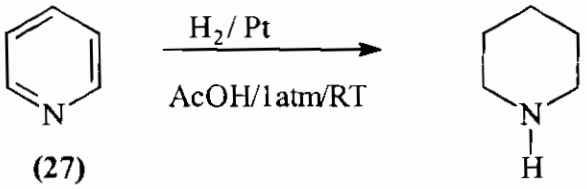
Scheme 7 Intermediates in the nucleophilic displacement of X^- by Y^- in X-substituted pyridine.

As well as nucleophilic and electrophilic substitution pyridine **(27)** can undergo free radical substitution. Radical substitution reactions are unselective however in pyridines substitution usually takes place preferentially at the 2-position. If the reaction is carried out in an acid medium the selectivity is high and 4-cyanopyridine can be selectively substituted in good yield at the 2-position in acidic media by nucleophilic alkyl and acyl radicals as illustrated in scheme 8[27].



Scheme 8 Selective homolytic substitution of 4-cyanopyridine

The pyridine ring is generally resistant to oxidising agents. Pyridine is much more readily reduced than benzene and catalytic reduction usually proceeds to completion (95% yield) at atmospheric pressure and ambient temperature, as shown in scheme 9[28].

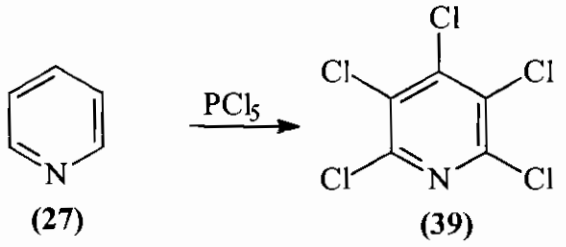


(27) (38)

Scheme 9

1.4.3 Synthesis of pyridine

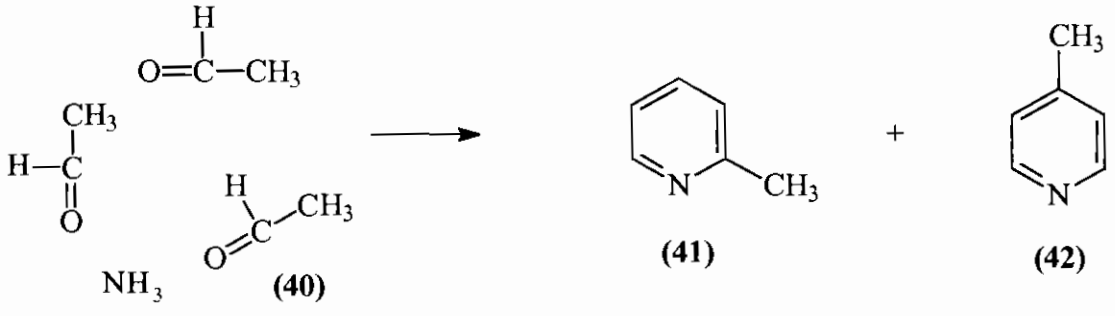
Pentachloropyridine **(39)** is generally prepared starting from pyridine **(27)** or one of its derivatives as shown in scheme 10.



(27) **(39)**

Scheme 10

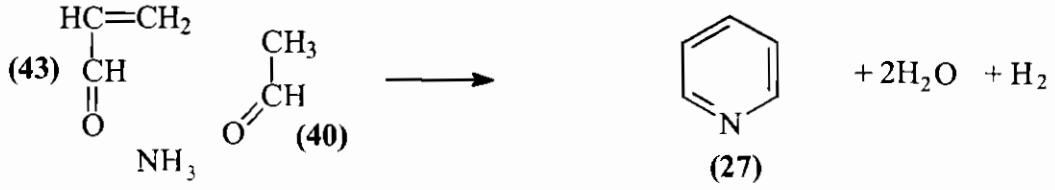
Several methyl- and ethylpyridines can be obtained from the volatile mixture resulting from the carbonisation of coal. Coal tar contains about 0.2% of a mixture of pyridine bases, which are extracted with acid and then separated. This source has been superseded by large-scale synthetic routes to pyridine **(27)** and methylpyridines from aliphatic starting materials. The reaction of aldehydes or ketones with ammonia is the most general synthetic process for the manufacture of pyridine bases. This reaction was first studied in detail by Chichibabin in 1924[29]. The reaction is usually carried out at 350-550°C in the presence of a solid acid catalyst[30]. For example acetaldehyde **(40)** and ammonia give 2-methlypyridine **(41)**, and 4-methylpyridine **(42)**, as illustrated in scheme 11.



(40) **(41)** **(42)**

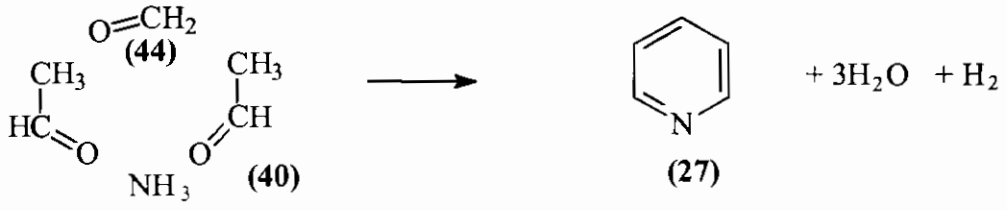
Scheme 11

Acrolein **(43)** and acetaldehyde **(40)** react with ammonia mainly to form pyridine **(27)**, as shown in scheme 12.



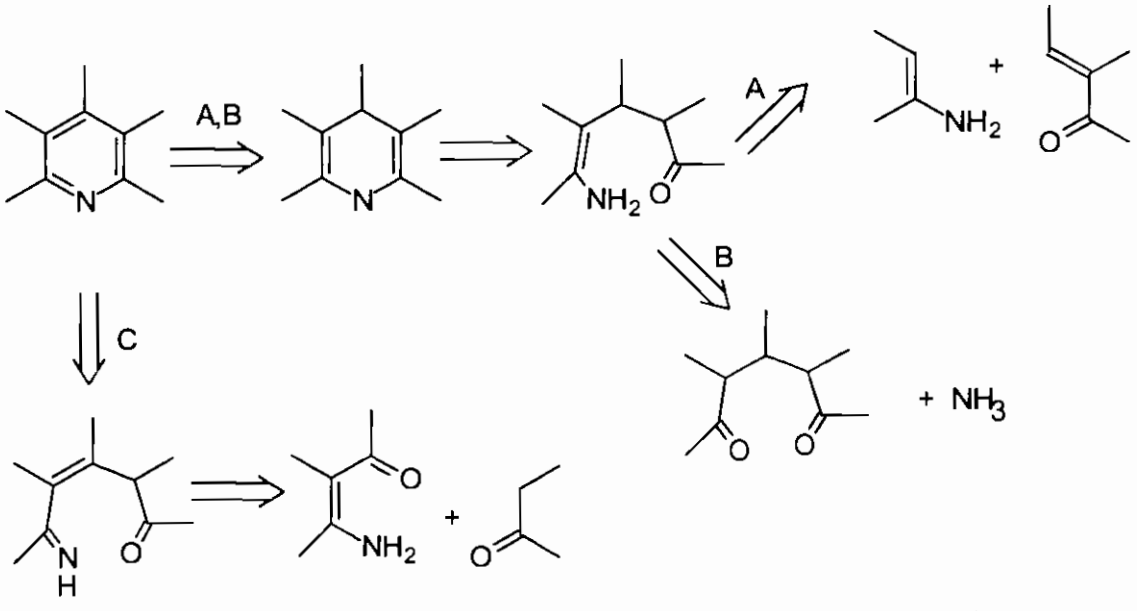
Scheme 12

Acetaldehyde **(40)** and formaldehyde **(44)** react with ammonia to give mainly pyridine **(27),** as shown in scheme 13 and is one of the most widely used methods for pyridine production.



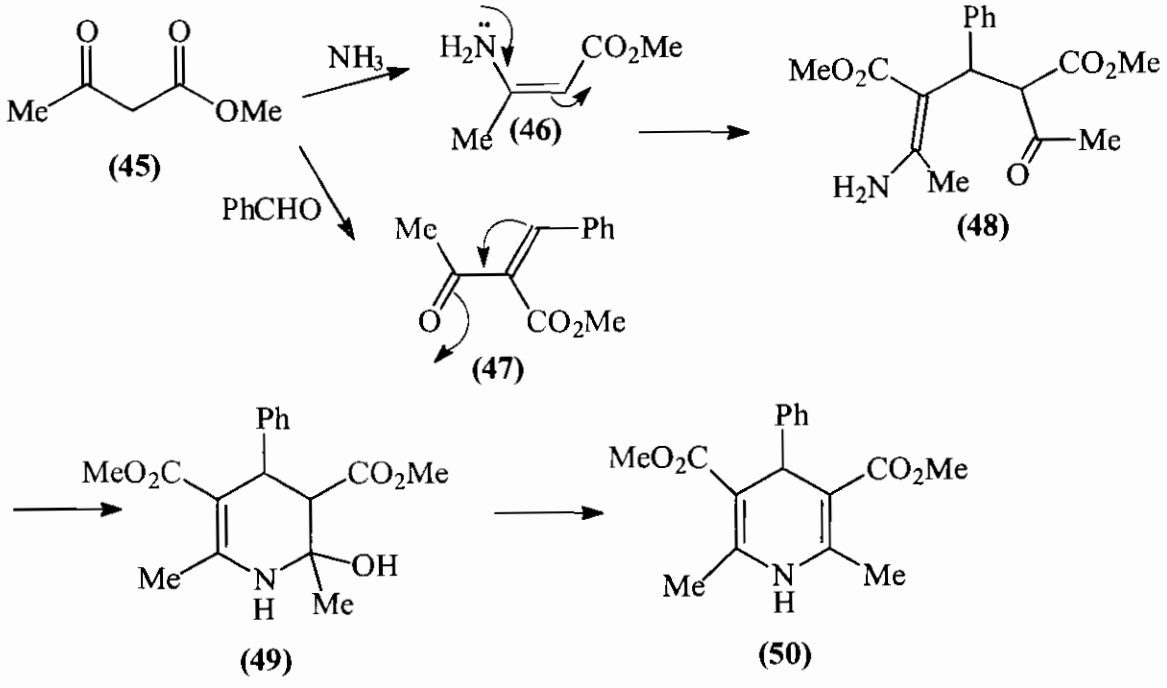
Scheme 13

The retrosynthetic analysis of the pyridine ring system illustrated in scheme 14 shows three possible ways of making the ring from readily available materials. All three methods, and many related methods, are used to prepare pyridine.



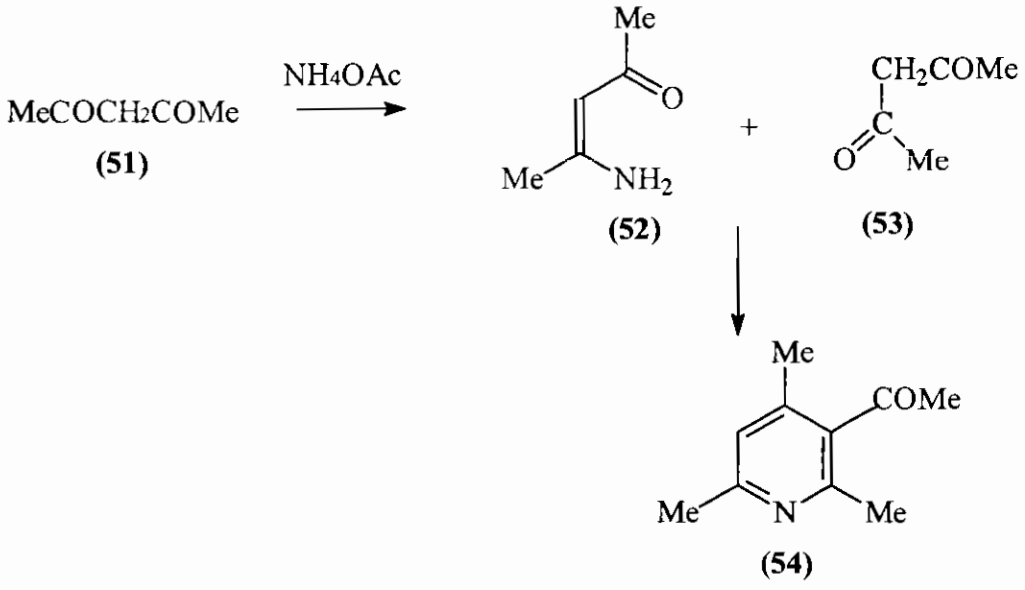
Scheme 14 Disconnection analysis of three cyclisation routes to pyridine

An example of route A is the Hantzsch synthesis where 1,3-dicarbonyl compounds react with aldehyde and ammonia to yield 1,4-dihydropyridines [31]. This reaction has been widely used for the synthesis of dihyropyridine and pyridines with symmetrical substitution patterns. The reaction and its mechanism are illustrated in scheme 15. Four compounds participate in the reaction, in this example there are 2 moles of methyl acetoacetate **(45)**, benzaldehyde and ammonia. Two intermediates are produced by separate reaction of methyl acetoacetate **(45)** with ammonia and with benzaldehyde to give methyl 3-aminobut-2-enoate **(46)** and an unsaturated ketoester **(47)** respectively. These two intermediates then combine to form the adduct **(48)** which undergoes cyclisation to form the dihydropyridine **(50)** via the intermediate **(49)** which can be aromatised by oxidation with nitric acid or with nitric oxide.



Scheme 15

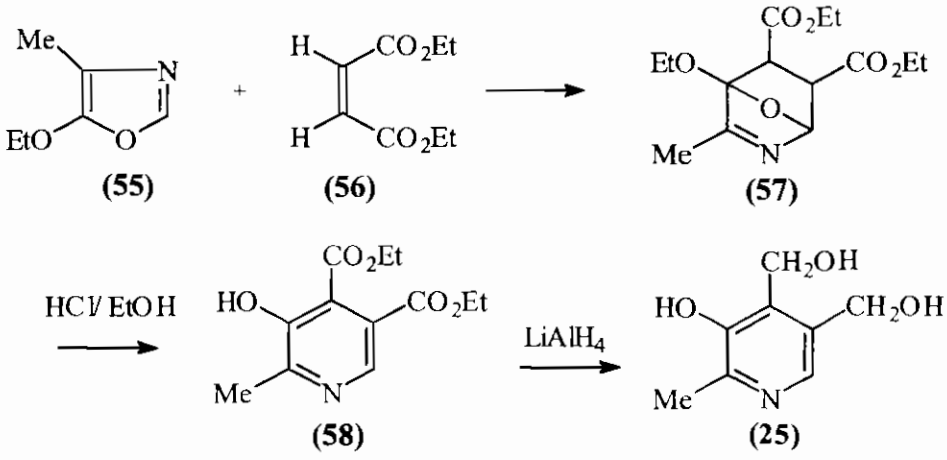
Route C of the retrosynthetic scheme 14, is also well known as a method for the preparation of pyridines and an example is shown in scheme16.



Scheme 16 Formation of 3-acetyl-2,4-6-trimethylpyridine (54) from pentane-2,4-dione (51) and ammonium acetate.

Route B in scheme 14 involves the cyclisation of 1,5-diketones with ammonia and is of rather limited use.

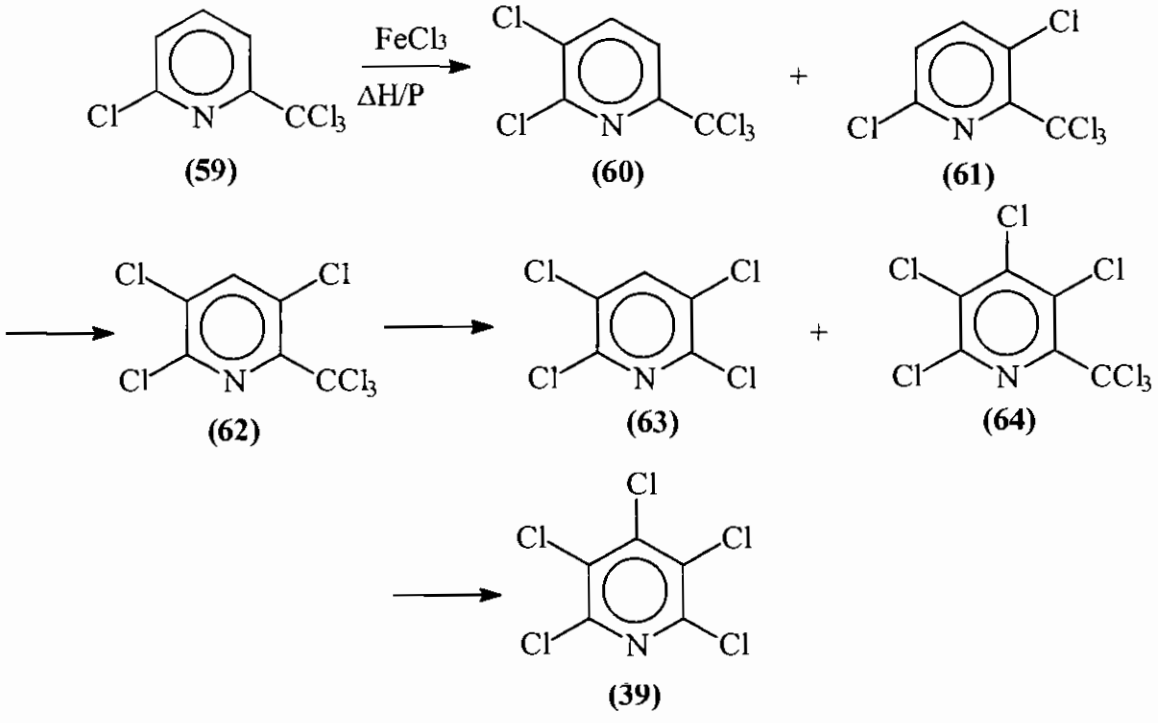
Pyridine rings can also be prepared via [4 + 2] cycloaddition reactions. These Diels Alder reactions are particularly useful for producing partially reduced pyridines. The most useful of these Dicls Alder reaction involves oxazoles as the diene component and reactions of this type provide the simplest routes to the pyridoxine vitamins **(25)** as show in scheme 17



Scheme 17

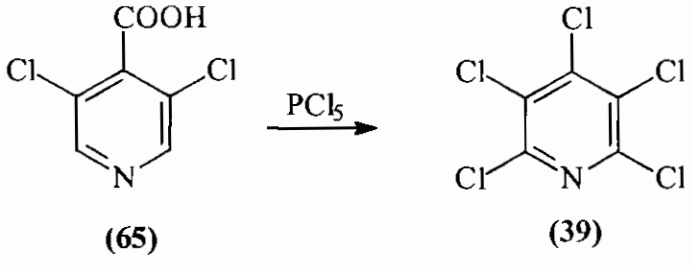
Synthesis of pentachloropyridine:

The introduction of a halogen substituent into the pyridine ring may be achieved in several ways. Halogenation of pyridines generally gives a mixture of chlorinated pyridines. However exhaustive chlorination of pyridines gives pentachloropyridine. The reaction process is illustrated in scheme 18.[32]



Scheme 18

It has becn reported that pentachloropyridine can be prepared from dichloroisonicotinic acid **(65)** and phosphorus pentachloride at 300°C as illustrated in scheme 19 [33] but no yields have been quoted.

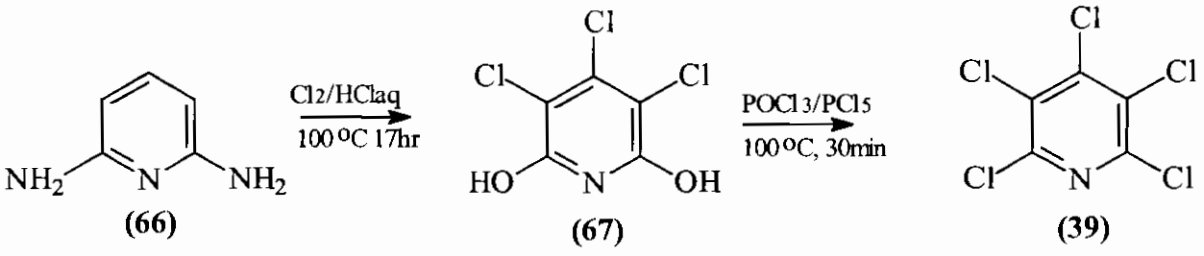


Scheme 19

Pentachloropyridine **(39)** can also be prepared from pyridine **(27)** and phorphoruspentachloride, as reported by Sell[34] in 1898. Banks in 1965 reported a similar synthesis using a reaction ratio of 12:1 PCl_5: C_5H_5N, at 350°C under pressure for 12-14 hours, yielding a product that on steam distillation afforded almost pure

pentachloropyridine **(39)** in 97% yield[35]. This process is not satisfactory for the economical preparation of substantial quantities of pentachloropyridine **(39)**.

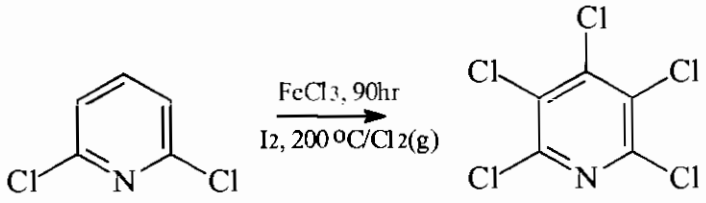
Flowers reported that pentachloropyridine can be prepared from the chlorination of commercially available 2,6-diaminopyridine **(66)** in hydrochloric acid solution which gives 3,4,5-trichlorodihydroxypyridine **(67)** followed by treatment with a mixture of phosphorus oxychloride and phosphorus pentachloride to yield pentachloropyridine **(39)**[36],as shown in scheme 20



(66) **(67)** **(39)**

Scheme 20

A US patent 3538100 describes the preparation of pentachloropyridine **(39)** in yields of 84% from 2,6-dichloropyridine **(68)**, a cheap and economical reactant, with chlorine gas in the presence of a catalyst, at 200°C[37],as shown in scheme 21.



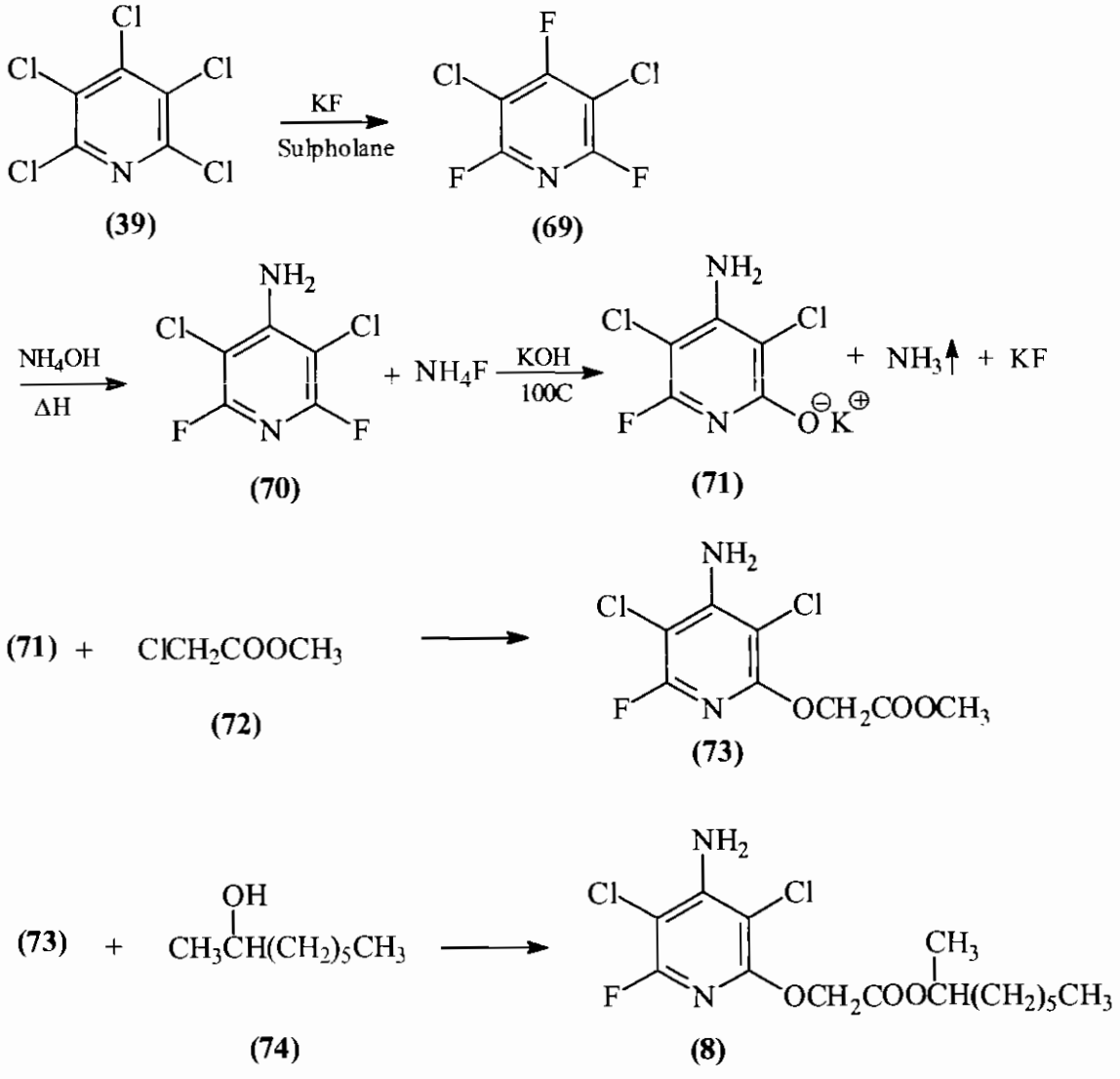
(68) **(39)**

Scheme 21

There are many other methods of little commercial use as low yields of pentachloropyridine **(39)** are obtained.

1.5 Literature review of synthesis of fluroxypyr and intermediates

The proposed synthesis of fluroxypyr **(8)** was based on a technical bulletin[38] from Agriguard Ltd. This process starts from pentachloropyridine **(39)** via 3,5-dichloro-2,4,6-trifluoropyridine **(69)**. The 3,5-dichloro-2,4,6-trifluoropyridine **(69)** is then converted into potassium 4-amino-3,5-dichloro-6-fluoro-pyridinate **(71)** by treatment with ammonia and then potassium hydroxide. The potassium salt is then treated, without isolation, with methyl chloroacetate **(72)** to form methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73).** This is then converted into 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** (fluroxypyr) by treatment with 2-octanol **(74)** as illustrated in scheme 22.



Scheme 22

3,5-Dichloro-2,4,6-trifluoropyridine **(69)** can be prepared by the so called 'Halex' fluorination reaction[39]. The reaction of pentachloropyridine **(39)** with KF in a 1:5.9 mole ratio suspended in sulpholane at 220°C gives 3,5-dichloro-2,4,6-trifluoropyridine **(69)** in an 87% yield [40]. 3,5-Dichloro-2,4,6-trifluoropyridine **(69)** has also been prepared by the reaction of pentachloropyridine with KF in a 1:11 mole ratio at 400°C for 18 hours in the absence of a solvent giving 84% yields of 3,5-dichloro-2,4,6-trifluoropyridine **(69)**[41]. It has also been reported that the reaction of pentachloropyridine and KF in 1-methyl-2-pyrrolidinone gives yields of 65% [35] and 90% of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** when using a mole ratio of 1: 3.18[42].

Of these methods two where chosen for the current investigation. The first involved the reaction of pentachloropyridine with KF in a 1:5.9 mole ratio in sulpholane at 220°C[40]. The second method by Banks [35], involved the reaction of pentachloropyridine with KF in 1-methyl-2-pyrrolidinone. The reaction described in the US patent 4746749 was not attempted as the industrial equipment involved was unavailable for the preparation of 3,5-dichloro-2,4,6-trifluoropyridine **(69).**

The second stage of the reaction involves the synthesis of potassium-4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** via 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** as reported by the Dow chemical company[43]. In the preparation of potassium-4-amino-3,5-dichloro-6-fluoro-2-pyridinate from 3,5-dichloro-2,4,6-trifluoropyridine **(69)**, ammonation and hydrolysis reactions were conducted consecutively without removal of the ammonium fluoride produced in the ammonation. Sufficient aqueous potassium hydroxide was added in the hydrolysis procedure to convert the ammonium fluoride to ammonia and potassium fluoride, as well as to hydrolyse the 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** to potassium-4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71).** The aqueous mixture of potassium fluoride and potassium-4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** was separated and recovered by the addition of a dipolar aprotic solvent.

The third and fourth stages of the reaction, the preparation of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy)acetate **(73)** and it's transesterification to 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was carried out by the method reported by Dowelanco[44]. The methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** was prepared by the alkylation of potassium-4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** with methyl chloroacetate in 94.8%

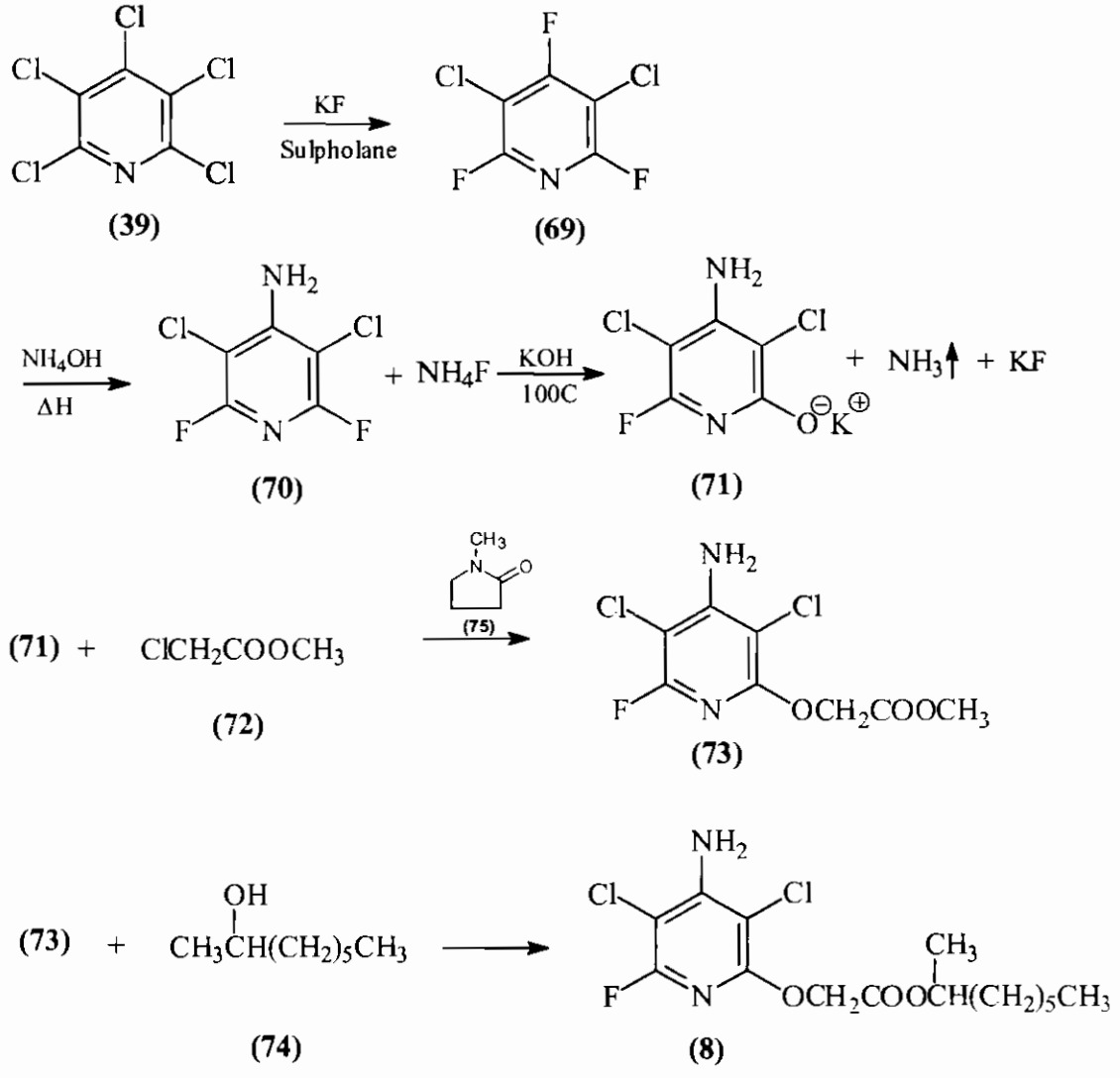
yield[44]. The final product 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (fluroxypyr) **(8)** was then prepared from methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy)acetate **(73)** by a transesterification reaction in the presence of a catalyst in 97.4% yield[44] as shown in scheme 22.

The subject of this thesis was the bench synthesis of fluroxypyr **(8)**, the scale-up of the reaction, the analysis of the technical material and the synthesis of impurities

Chapter 2
Results and Discussion

2.0 Synthesis of fluroxypyr

Fluroxypyr, 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was synthesised starting from pentachloropyridine **(39)** in a 4 stage process, as shown in scheme 22.

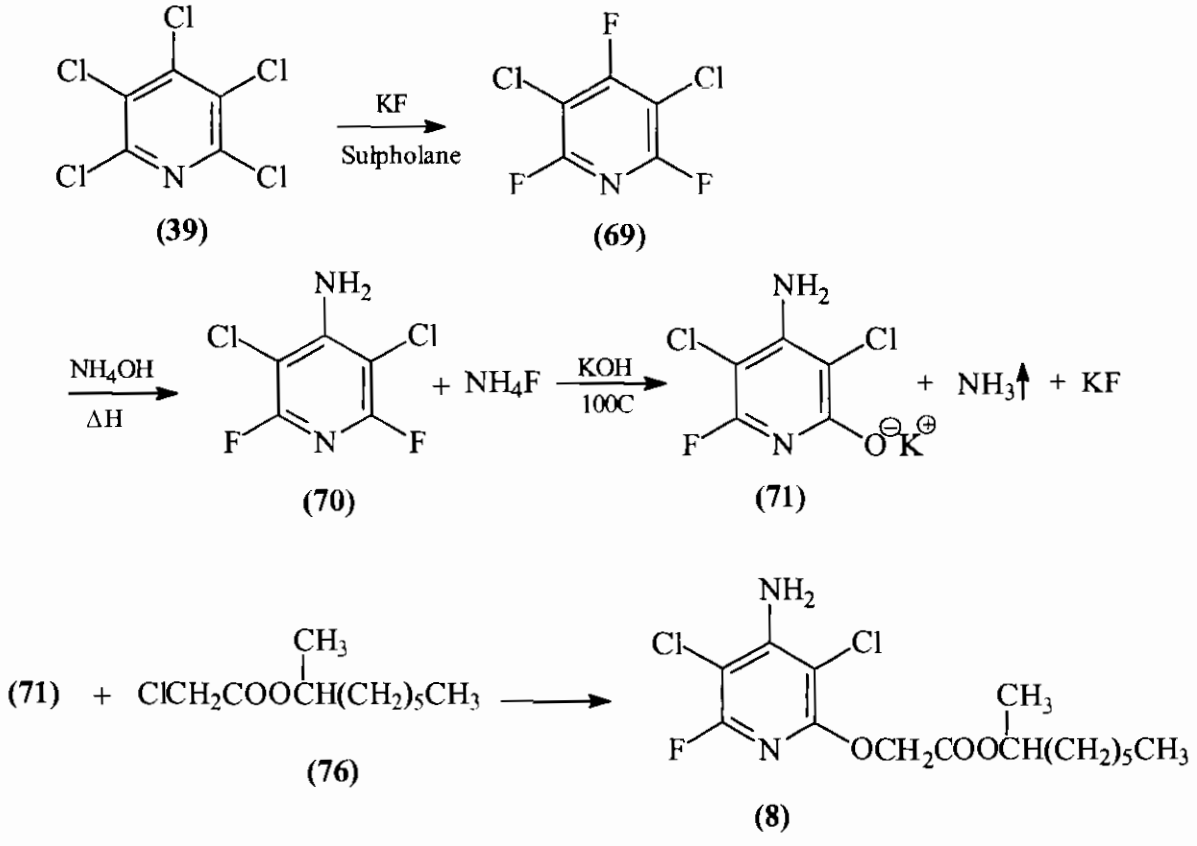


Scheme 22

The first reaction investigated involved a nucleophilic substitution reaction involving the conversion of pentachloropyridine **(39)** to 3,5-dichloro-2,4,6-trifluoropyridine **(69)** using potassium fluoride in sulpholane. An additional reaction was investigated utilising potassium fluoride in N-methyl-2-pyrrolidione (NMP) **(75)** for the synthesis of 3,5,-dichloro-2,4,6-trifluoropyridine **(69)** but the yield showed no improvement, there was a problem with the work-up of the reaction mixture.

The second stage investigated the conversion of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** to potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** via 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)**[43]. Potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** has been prepared and isolated although the isolation of it was not necessary for the successful synthesis of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)**. Potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** was not isolated as the same solvent was employed in the next stage. Potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** in NMP **(75)** was then alkylated to yield methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)**[44]. The final stage of the reaction sequence involved the transesterification of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 1-methylheptyl (4-amnio-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)**[44].

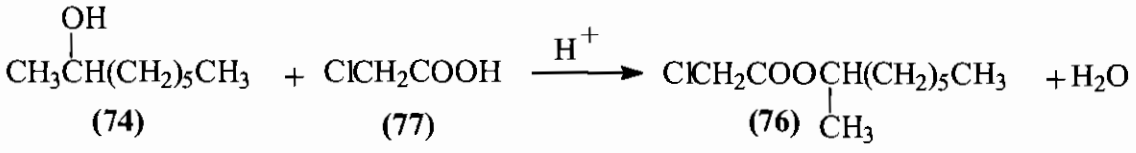
An alternative route to the synthesis of fluroxypyr was also investigated, and involved a 3 stage process as shown in scheme 23.



(39) (69) (70) (71) (76) (8)

Scheme 23

The first two stages were the same as in the first route investigated for the synthesis of fluroxypyr. The third stage differs in that fluroxypyr is prepared directly from potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** by alkylation with 1-methylheptyl chloroacetate **(76)**. 1-Methylheptyl chloroacetate **(76)** is not commercially available and was prepared by the condensation reaction of 2-octanol **(74)** with chloroacetic acid in the presence of a catalyst[45], as shown in scheme 24



Scheme 24

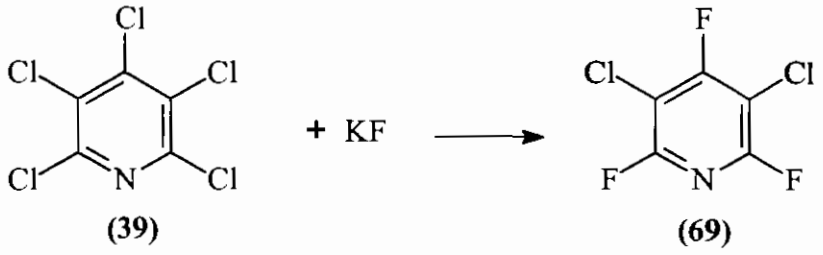
The experimental part of this work was carried out in the following stages;

a) optimisation of the yield and reaction conditions for the synthesis of fluroxypyr and its intermediates
b) the scale up of the reaction process to a two litre scale
c) the synthesis of fluroxypyr by an alternative method and
d) the identification and synthesis of impurities present and reported to be present in technical fluroxypyr.

Fluroxypyr, the intermediate products and impurities prepared were isolated and characterised by NMR, FTIR, HPLC, melting point and elemental analysis.

2.1 Discussion of stage 1, the synthesis of 3,5-dichloro-2,4,6-trifluoropyridine (69) from pentachloropyridine (39).

The synthesis of 3,5-dichloro-2,4-6-trifluoropyridine **(69)** from pentachloropyridine **(39)** as shown in scheme 25 was investigated using two different aprotic dipolar solvents.



(39) **(69)**

Scheme 25

The first series of reactions (using sulpholane as solvent) were concerned with the optimisation of reaction conditions for stage one, the synthesis of 3,5-dichloro-2,4,6-trifluoropyridine **(69)**. The stochiometric ratio, needed to convert pentachloropyridine **(39)** to 3,5-dichloro-2,4,6-trifluoropyridine **(69)**, was 1:3 pentachloropyridine **(39)** to potassium fluoride. The literature recommended using an excess of potassium fluoride between 1.5 to 2.5 moles of potassium fluoride per atom of chlorine to be replaced. In the example given a 1:5.8 molar ratio of pentachloropyridine **(39)** to potassium fluoride was used resulting in a yield of 87% of 3,5-dichloro-2,4,6-trifluoropyridine **(69)**. The reaction conditions reported were $4^1/_2$ hours at 192°C and the product was recovered by distillation.

The first stage of the synthesis involved the preparation of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** from pentachloropyridine **(39)** and potassium fluoride in sulpholane[40]. The reaction was monitored using HPLC and from the reaction profile obtained the reaction reaches a maximum yield of 70% after 30 minutes. Further refluxing reduces the yield of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** but increases the yield of monochlorotetrafluoropyridine **(78)** which is a known by-product of this reaction[40]. The 70% yield reported above is lower than that reported in the literature (87%)[40] and therefore it was attempted to obtain better yields by varying the amount of solvent used and the reaction ratio of potassium fluoride to pentachloropyridine **(39)**.

In a subsequent attempt to prepare 3,5-dichloro-2,4,6-trifluoropyridine **(69)** the amount of solvent used was decreased from 250g to 200g keeping the ratio of pentachloropyridine **(39)** to potassium fluoride at a ratio of 1:5.9 and this resulted in an

increased yield of 74%. A further decrease in the amount of solvent (using the same ratio of reagents as above) was not possible as the mixture became too viscous and stirring was inhibited. On decreasing the reaction ratio of pentachloropyridine **(39)** to potassium fluoride from 1:5.9 to 1:5.0 with all other reaction conditions being constant resulted in an improved yield of 76% of 3,5-dichloro-2,4,6-trifluoropyridine **(69)**. A further decrease of the molar ratio of pentachloropyridine **(39)** and potassium fluoride was attempted and a 1:4 ratio gave a 31% yield of 3,5-dichloro-2,4,6-trifluropyridine **(69)**. From the above results it can been seen that the optimum ratio of pentachloropyridine **(39)** to potassium fluoride is 1:5. As the ratio of pentachloropyridine **(39)** to potassium fluoride was decreased (from 1:5.9 to 1:5) it was decided to try and decrease the amount of solvent used.

The amount of solvent used was decreased from 200g to 150g using the lower reaction ratio of 1:5 pentachloropyridine **(39)** to potassium fluoride and this yielded 75% of 3,5-dichloro-2,4,6-trifluoropyridine **(69)**.

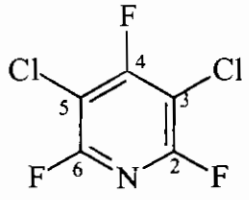
In a further reaction 3,5-dichloro-2,4,6-trifluoropyridine **(69)** was prepared using N-methyl-2-pyrrolidinone **(75)** (NMP) as solvent and the optimum reaction conditions and ratios found above were employed for this reaction. The reaction was monitored using HPLC and as before after 30 minutes reaction had reached maximum yield. The distillate collected for the reaction was not pure 3,5 dichloro-2,4,6-trifluoropyridine **(69)** but was a mixture of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** and N-methyl-2-pyrrolidinone **(75)**. This was due to the boiling points of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** and NMP **(75)** being very close resulting in difficulty in separation on distillation.

Although none of the yields obtained were as high as those obtained by the yields reported in the literature[40] (87% yield), the 9-fold decrease in reaction time compensated for the lower yield. In the $500cm^3$-scale utilising pentachloropyridine **(39)** (50grams) the optimum conditions involved the employment of sulpholane as the solvent, and a ratio of sulpholane to pentachloropyridine **(39)** to potassium fluoride of 5.65:1:5. The reaction temperature was 200°C and the reaction time was 30 minutes with mechanical stirring.

Spectral analysis on 3,5-dichloro-2,4,6-trifluoropyridine **(69)** showed peaks in the IR at $1055cm^{-1}$ for C-F and at $788cm^{-1}$ for C-Cl. The ^{13}C NMR is complicated by the fact that fluorine has a spin quantum number of ½ and therefore couples with the

carbons in 3,5-dichloro-2,4,6-trifluoropyridine (**69**) causing the carbon peaks to be split, with the following coupling constant.

δ_c(50MHz; $CDCl_3$) 164.252ppm (dt, C_4), JC_4-F_4 265.7Hz, C_4-F_2 (C_4-F_6) 5.35Hz; 155.256ppm (ddd C_2 and C_6), JC_6-F_6 (C_2-F_2) 246.6Hz, C_6-F_2 (C_2-F_6) 6.9Hz, C_6-F_4 (C_2-F_4) 17.2Hz; 103.907ppm (m, C_3 and C_5), JC_3-F_2 (C_5-F_6) 41.5Hz, C_3-F_4 (C_5-F_4) 20.8Hz[46], (figure 2.1.1)

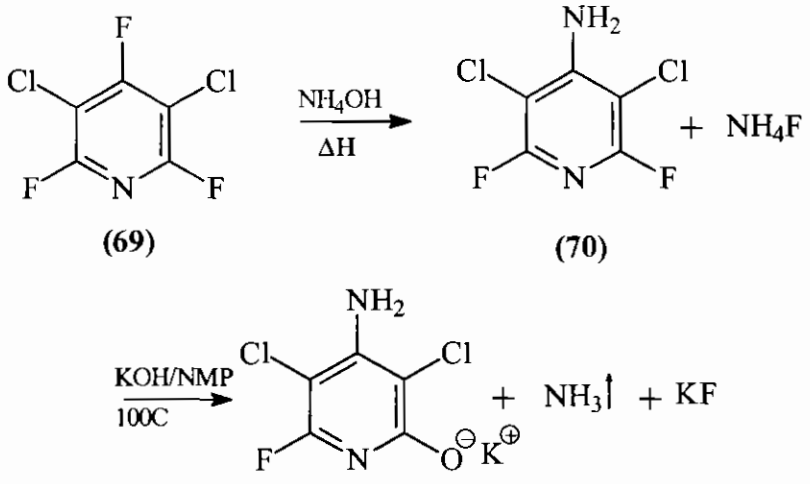


(69)

Figure 2.1.1

2.2 Discussion of stage 2, the synthesis of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (71) from 3,5-dichloro-2,4,6-trifluoropyridine (69).

The second stage of the process involves ammonation followed by the hydrolysis without the removal of the ammonium fluoride produced in the ammonation of 3,5-dichloro-2,4,6-trifluoropyridine (**69**) as shown in scheme 26.



(69) **(70)** **(71)**

Scheme 26

The ammonation reaction was initially carried out using 35% ammonia solution according to the literature[43] and then by using 28% ammonia solution. The hydrolysis reaction was initially carried out using potassium hydroxide solution (50%) and then using a 40% solution which is the concentration commercially available. Table 2.2.1 gives yields of potassium 4-amino-3,5-dichloro-2,4,6-trifluoropyridine (**71**), as recorded using HPLC, for the different strengths of ammonia and potassium hydroxide solutions used.

RATIO DCTF	RATIO NH_3	% NH_3	RATIO KOH	% KOH	HPLC YIELD%
1	3	35	3	50	93.4
1	3	25	3	50	90.0
1	3	25	3	40	97.0

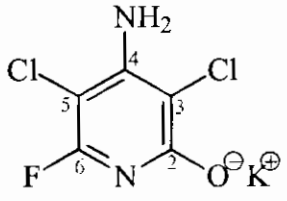
Table 2.2.1

The ratio needed to replace one fluorine atom with one NH_2 moeity is 1:1, however a molar ratio of 1:3, 3,5-dichloro-2,4,6-trifluoropyridine (**69**) to ammonia was

employed. An excess of potassium hydroxide was used in the reaction, as excess aqueous potassium hydroxide was needed to convert the ammonium fluoride produced in the ammonation reaction to ammonia. In addition the excess potassium hydroxide was used to hydrolyse 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** to potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (**71**). The excess ammonia was removed as a gas by heating.

The separation of potassium fluoride and potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (**71**) was achieved when the aqueous mixture containing both was combined with a sufficient amount of a water soluble dipolar, aportic solvent (N-methyl-2-pyrrolidinone) to form two liquid phases. The bottom phase contained most of the water and the potassium fluoride and the other layer contained the dipolar aprotic solvent and potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)**[43]. The two phases were separated by decantation and any remaining water in the organic phase was separated by distillation.

The potassium salt (**71**) was also isolated by distillation of solvent to yield a light brown solid, which decomposed on heating. Spectral analysis in the ^{1}H NMR (d-DMSO) showed a broad peak at δ5.254ppm (NH_2). The ^{13}C NMR also showed the effect of carbon fluorine coupling and had the following peaks and coupling constants. δ_c(50MHz, DMSO) 163.192ppm (d, C_2) JC_2-F_6 21Hz, 156.159ppm (d, C_6) JC_6-F_6 221.6Hz, 148.162ppm (d, C_4) JC_4-F_6 8Hz, 97.315ppm (d, C_3) JC_3-F_6 8Hz, 78.939ppm (d, C_5) JC_5-F_6 43.1Hz, (figure 2.2.1)

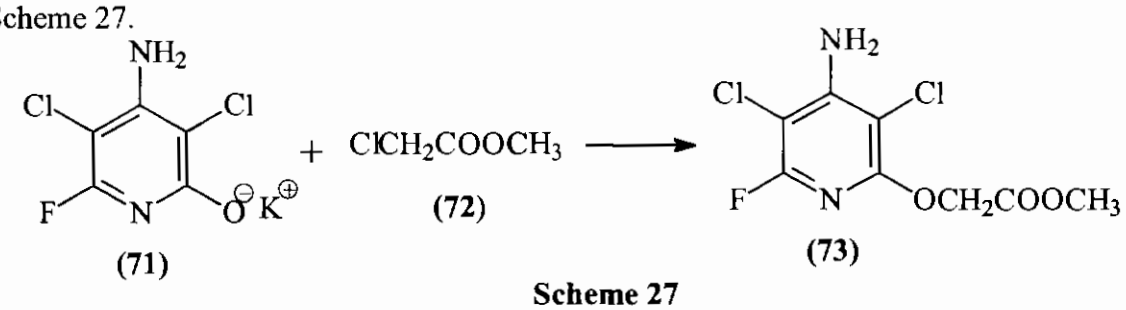


(71)

Figure 2.2.1

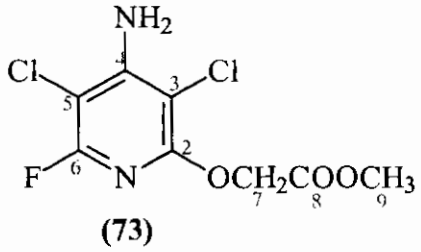
2.3 Discussion of stage 3, the synthesis of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) from potassium 4-amnio-3,5-dichloro-6-fluoro-2-pyridinate (71).

The third stage of the process involved the alkylation of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** with methyl chloroacetate **(72)**[44], as shown in Scheme 27.



Scheme 27

The ratio needed for the alkylation was a 1:1 ratio of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** to methyl chloroacetate (72) and a ratio of 1:1.1 was employed. The reaction was monitored using HPLC and from the profile obtained the reaction was seen to come to completion in 2 hours on a 250cm^3 scale involving 0.05 moles of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)**. The yield of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** was 80% with respect to 3,5-dichloro-2,4,6-trifluoropyridine **(69)**. The product had a melting point of 124.5-125.5°C. Spectral analysis showed peaks in the IR (KBr) at 3485cm^{-1} NH_2, 1755cm^{-1} C=O. ^{1}H NMR spectra showed peaks at δ 5.196ppm (2H, broad, NH_2), 4.877ppm (2H, s, OCH_2), 3.758ppm (3H, s, $OOCH_3$). The ^{13}C NMR shows the effect of the presence of a fluorine atom in the molecule. The presence of fluorine causes n+1 splitting of the carbon peak where n is the number of adjacent fluorine atoms. The peaks and coupling constants for methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** are as follows: δ_{13} 168.886 (C=O, C_8), 155.279 (d, C_6) JC_6-F_6 234.6Hz, 154.423 (d, C_2), JC_2-F_6 16.8Hz, 150.651 (d, C_4), JC_4-F_6 5.7Hz, 96.923ppm (d, C_3) JC_3-F_6 5.4Hz, 93.941 (d, C_5) JC_5-F_6 38.15Hz, 63.048 ($O\underline{C}H_2$, C_7), 52.183 ($OO\underline{C}H_3$, C_9) ppm (figure 2.3.1).

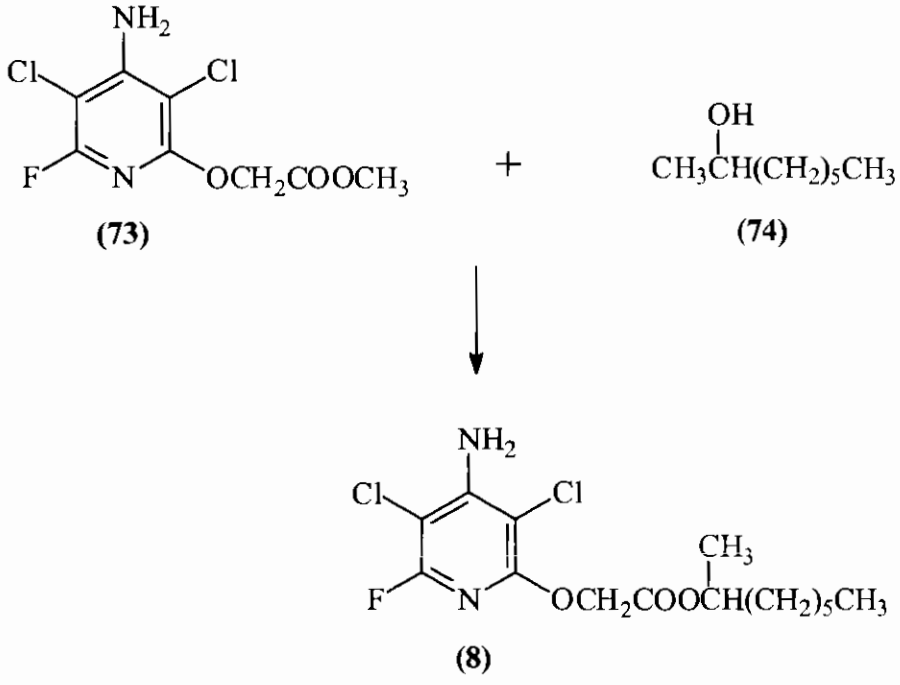


(73)

Figure 2.3.1

2.4 Discussion of stage 4, synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (8) from methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73).

The fourth stage of the process involved the transesterification of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 1-methyl heptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** with 2-octanol **(74)** as shown in Scheme 28.



Scheme 28

The reaction ratio needed was 1:1 methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 2-octanol **(74),** but previous work[44] used a reaction ratio of 1:4.7 and this was utilised in this reaction . The reaction was conducted under pressure and in the presence of a catalyst. The reaction time was 4 hours using 50 grams of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73).**

1-Methylheptyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was prepared using the reaction conditions described by Dow Elanco[44]. The reaction was not monitored as it was not possible to sample the reaction while it was under pressure. A yield of 56% of 1-methylheptyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was obtained after recrystallisation from 40-60 petroleum ether.

As the reaction could not be monitored while under pressure, the reaction was carried out at normal atmospheric conditions and was monitored using HPLC. From the HPLC profile obtained the reaction time was 1 hour when using a 10gram scale of methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** and yielded 92% 1-methylheptyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** as a light brown solid.

In the reaction above a ratio of 1:5.4 methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 2-octanol **(74)** was employed. However as mentioned earlier the minimum ratio of methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 2-octanol **(74)** needed is 1:1. Therefore a series of reaction were carried out to determine the minimum reaction ratio for the maximum yield and the results are shown in table 2.4.1. All reactions were monitored using HPLC and the catalyst employed was tetrabutyl titanate.

Ratio of MFE* used	Ratio of 2-octanol used	Time in hours	HPLC % conversion	Yield %
1	1	1	No reaction	N/A
1	2	1	94	88
1	3	1	94	93
1	4	1	93	92

* MFE= methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73)

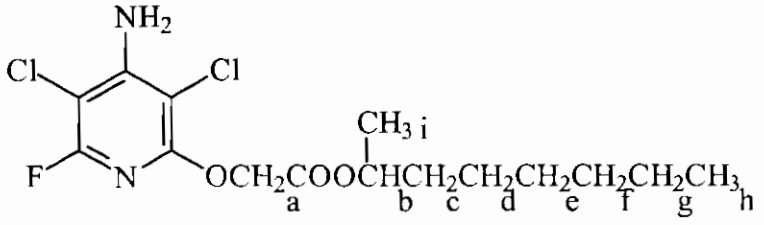
Table 2.4.1

From the above results it was concluded that optimum reaction ratio of methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 2-octanol **(74)** was 1:3. The catalyst employed tetrabutyl titanate, was not isolated from the final reaction product **(8)**. The preparation of 1-methylheptyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was carried out without the use of a catalyst. The reaction was monitored using HPLC and from the reaction profile it was seen that after 10 hours only 6% of methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** was converted to 1-methylheptyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)**. From this it was concluded that for the transesterifiacation reaction to proceed a

catalyst must be employed. Suitable catalysts include tetrabutyl titanate and strong acids such as sulphuric acid and p-toluenesulphonic acid (PTSA)[44].

Utilising sulphuric acid or PTSA as the catalyst, the reactions were carried out using a reaction ratio of 1:3 methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (**73**) to 2-octanol (**74**), at a reaction temperature of 180^{O}C and yields of 92% were recorded using HPLC, without product isolation. The reason no product was isolated was that the acid catalysts were not removed from the reaction product before the isolation of the product. The presence of the acid catalyst during the removal of 2-octanol (**74**) caused the decomposition of the reaction product by ester hydrolysis. To avoid this the acid catalyst must first be removed before the isolation of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (**8**). However when using tetrabutyl titanate the first catalyst there was no need for the removal of the catalyst before the isolation of the product (**8**) as no ester hydrolysis was observed with this catalyst. Therefore it was concluded that tetrabutyl titanate was the best catalyst to use in the reaction.

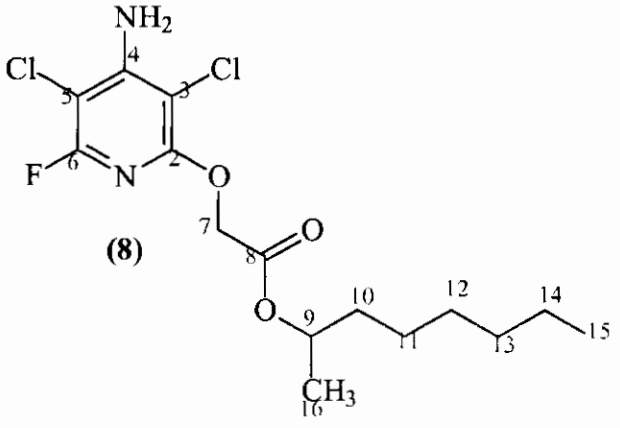
Spectral analysis of (**8**) (figure 2.4.1) showed peaks in the IR spectra (KBr) at 3351cm^{-1} (NH_2), 2960-2853cm^{-1} (CH), 1745cm^{-1} (C=O), 1625-1451cm^{-1} (C=C, C=N ring stretching skeletal bonds), 1148cm^{-1} (C-F), 775cm^{-1} C-Cl. The ^{1}H NMR spectra of (**8**) shows 6 peaks, δ5.21 (2H, broad, NH_2), 4.968 (1H, sextet, CH-b), 4.807 (2H, s, CH_2-a), 1.525 (2H, m, CH_2-c), 1.205 (11H, m, CH_2-d,e,f,g, CH_3-i), 0.845 (3H, t, CH_3-h) ppm.



(**8**)

Figure 2.4.1

The ^{13}C NMR spectra showed peaks at δ168.10 (C=O, C_8), 155.278 (d, C_6) JC_6-F_6 234.6Hz, 154.557 (d, C_2) JC_2-F_6 16Hz, 150.608 (C_4) JC_4-F_6 5.3Hz, 96.877 (d, C_3) JC_3-F_6 5.3Hz, 93.80 (d, C_5) JC_5-F_6 37.8Hz, 72.50 (O<u>C</u>H, C_9), 63.494 (O<u>C</u>H_2, C_7), 35.718 (CH-<u>C</u>H_2, C_{10}), 31.584 (<u>C</u>H_2, C_{13}, 28.951 (<u>C</u>H_2, C_{12}), 25.066 (<u>C</u>H_2, C_{11}), 22.456 (<u>C</u>H_2, C_{14}), 19.733 (CH-<u>C</u>H_3, C_{16}), 13.936 (CH_2<u>C</u>H_3, C_{15}) ppm, see figure 2.4.2 . A Dept spectra confirmed the presence of $2CH_3$, $6CH_2$ and 1CH group corresponding to **(8)** (figure 2.4.2). In addition six lines corresponding to the six quaternary carbons (C_2, C_3, C_4, C_5, C_6, C_8) were absent as expected from the Dept spectra.

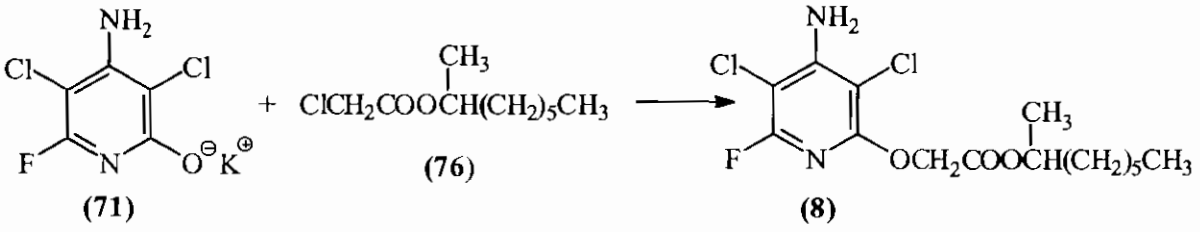


(8)

Figure 2.4.2

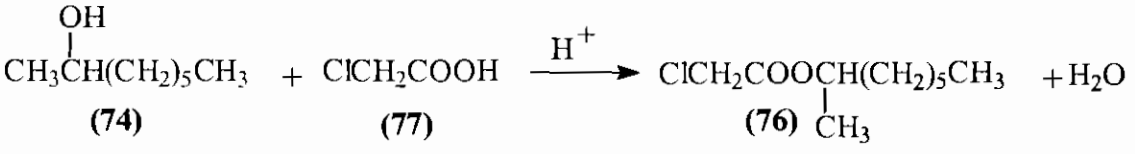
2.5 The alternative route to the synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (8).

This was a 3 stage process, stage one and two were common to both synthetic routes. The difference in the two routes was that in this route 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was prepared directly from potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** in NMP **(75)** as shown in scheme 29.



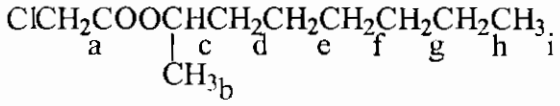
Scheme 29

This stage was similar to stage 3 in the Agriguard procedure except that potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** was alkylated using 1-methylheptyl chloroacetate **(76)** instead of methyl chloroacetate **(72)**. 1-Methylheptyl chloroacetate is not commercially available therefore it was prepared by the esterification of chloroacetic **(77)** acid with 2-octanol **(74)** in the presence of a catalyst[45], as shown in scheme 24. In esterification reactions an excess of either the acid or alcohol is employed, and excess the alcohol is used to shift the equilibrium to the right[47]. 1-Methyl heptylchloroacetate **(76)** was prepared using a reaction ratio of 1:1.6 of chloroacetic acid **(77)** to 2-octanol **(74)** with sulphuric acid as the catalyst as illustrated in scheme 24. The reaction was monitored by the amount of water removed by aid of a dean and stark apparatus. The product was recovered by fractional distillation in a yield of 65%.



Scheme 24

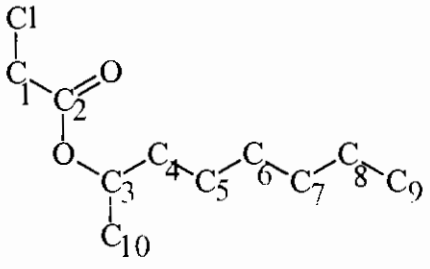
Spectral analysis of (**76**) showed peaks in the Ir spectra (neat) at 2940cm^{-1} (CH stretch), 1745cm^{-1} (C=O), 781cm^{-1} (C-Cl). The ^{1}H NMR spectra (200MHz, $CDCl_3$) showed peaks at 4.909 (1H, sextet, CH-c), 3.959 (2H, s, CH_2-a), 1.505 (2H, m, CH_2-d), 1.180 (11H, m, CH_2-e,f,g,h, CH_3-b), 0.808 (3H, t, CH_3-i) ppm, (figure 2.5.1).



(76)

Figure 2.5.1

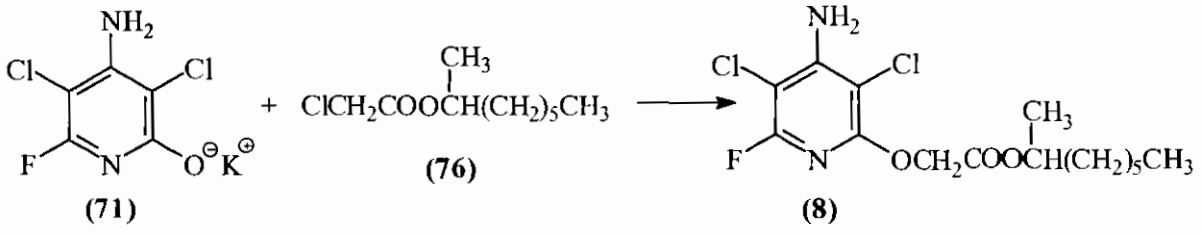
The ^{13}C NMR spectra (50MHz, $CDCl_3$) showed peaks at 166.801 (C=O, C_2), 73.253 (CH, C_3), 46.940 (CH_2, C_1), 35.493 (CH_2, C_4), 31.441 (CH_2, C_7), 28.789(CH_2, C_6), 24.970 (CH_2, C_5), 22.291 (CH_2, C_8), 19.484 (CH_3, C_{10}), 13.741 (CH_3, C_9) ppm, (figure 2.5.2). A DEPT experiment was run to aid in the elucidation of the ^{13}CNMR, the DEPT confirmed the presence of $2CH_3$, $6CH_2$ and 1CH as expected the line corresponding to the quaternary carbon (C_2) was absent.



(76)

Figure 2.5.2

1-Methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (**8**) was prepared by reacting 1-methylheptyl chloroacetate (**76**) with potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (**71**) in NMP (**75**) as illustrated in scheme 29 under the same reaction conditions used for stage 3 in the previous route (the preparation of methyl ester (**73**) (see section 2.3)).



Scheme 29

The reaction was monitored using HPLC and after 10 hours at 45^{O}C a 54% conversion of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** to 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** was obtained. Due to the low yield, the reaction was carried out at an increased reaction temperature 100^{O}C using a reaction ratio of 1:1.1 potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** to 1-methylheptyl chloroacetate **(76)**. This reaction was monitored using HPLC and from the reaction profile it was seen that an 82% conversion was reached after 1 hour at 100^{O}C. The work-up as before resulted in the formation of two layers. These layers were separated and the lower layer was distilled to remove the volatile components. The resultant viscous liquid solidified on cooling to yield a dark green solid which was recrystallised from hexane to yield 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** (41%) with a melting point of 55.9-56.9^{O}C (lit 56-57^{o}C)[48]. Spectral analyses are as reported previously in section 2.4. The overall yield in this process was 31%.

2.6 The Scale–up of the Agriguard process

Table 2.6.1 summaries the product yields for the Agriguard process (see scheme 22). The results of the scale-up are shown in table 2.6.2

	Scale (g) PCP*	Yield (g)	Yield %
Step 1	50	30.2	75
	100	60.79	76
	150	85.28	71
	300	164.3	68.4
	Scale (g) DCTF*	**Yield (g)**	**Yield %**
Step 2 (% based on HPLC)	25		92
	50		94
	100		95
	214		97
	Scale (g) potassium salt (71)	**Yield (g)**	**Yield %**
Step 3 (% yield based on moles DCTF* used in step2)		27	80
		52.2	78
		105.7	79
		231	80.85
	Scale (g) MFE*	**Yield (g)**	**Yield %**
Step 4	5	6.14	91
	10	12.28	90
	90	111.7	91
	220	281.5	93.8

* PCP = pentachloropyridine **(39)**, DCTF= 3,5-dichloro-2,4,6-trifluoropyridine **(69)** and MFE = methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)**

Table 2.6.1

Step	Scale (g) PCP*	Yield (g)	Yield %
1	300 + 100	164.3 + 60.7 = 225	70.4

Step	Scale (g) DCTF*	Yield (g)	Yield %
2	214		97% based on HPLC

Step	Scale	Yield (g)	Yield %
3	Based on step 2	231	80.85

Step	Scale (g) MFE*	Yield (g)	Yield %
4	220	281.5	93.8

*PCP = pentachloropyridine **(39)**, DCTF= 3,5-dichloro-2,4,6-trifluoropyridine **(69)** and MFE = methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)**

Table 2.6.2

The overall yield of fluroxypyr **(8)** in the Agiguard process was 47%, but a higher overall yield could be achieved if problems encountered in step one were overcome.

When the synthesis of fluroxypyr **(8)** was scaled up to a 2-litre scale requiring 300g of pentachloropyridine **(39)**, a number of difficulties were encountered. Using pentachloropyridine **(39)** in a 300g scale, in 480g of solvent, a viscosity problem was encountered and the stirring system employed was insufficient to stir the mixture efficiently. Additional solvent (150g) did not alleviate the problem resulting in a lower yield of product **(69)** (68%). On combining the product of this reaction with the product obtained from the 100g scale, 3,5-dichloro-2,4,6-trifluoropyridine **(69)** (225g) was available for further reaction. ^{13}C NMR and HPLC were used to confirm the purity of the products. .

3,5-Dichloro-2,4,6-trifluoropyridine **(69)** (220g) was converted into potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** as described previously in section 2.2.. The reaction was monitored using HPLC and from this it was found that the percent conversion was 97%. The product **(71)** was not isolated and the total volume of potassium 4-amino-3,5-dichloro-2,4,6-trifluorpyridine **(71)** in N-methyl-2-pyrrolidinone **(75)** was 1150cm^3 which was carried through to step three of the reaction process.

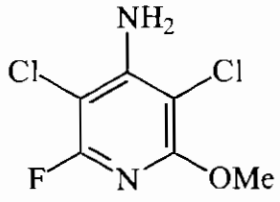
Potassium 4-amino-3,5-dichloro-2,4,6-trifluoropyridine **(71)** in N-methyl-2-pyrrolidinone **(75)** was dried by the removal of solvent (50g) to ensure that all residual

water was removed for the successful alkylation of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71).** Potassium 4-amino-3,5-dichloro-2,4,6-trifluorpyridine **(71)** was alkylated using methyl chloroacetate **(72)** (120g), in a 2 litre reaction vessel fitted with a mechanical stirrer and condenser. The reaction was montiored using HPLC and from this it was found that the reaction came to completion in 4 hours. The product was isolated by the removal of volatiles present and then by pouring the hot mixture into a 5-litre beaker containing water (1500cm^3). The mixture was allowed to cool to ensure all of the product had precipitated out. The product was collected by filtration and the wet cake obtained was dried in a vacuum oven to yield methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** in 80% yield.

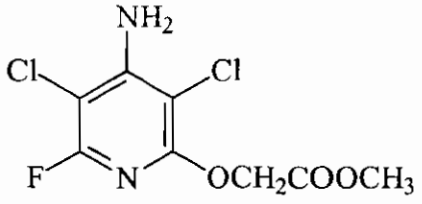
Methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** (220g) was converted to 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** by reaction with 2-octanol **(74)** in a 1-liter reaction vessel fitted with an overhead mechanical stirrer, fractionation column (30cm^3) with a distillation head and vacuum source. The reaction was monitored using HPLC and it was found that the reaction came to completion in 90 minutes. The product was isolated by the removal of the excess 2-octanol **(74)** under vacuum to yield a viscous liquid which solidified to a light brown solid 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** (281.63g, 93.8% yield) with a melting point of 56.4-57.3°C.

2.7 Synthesis of impurities

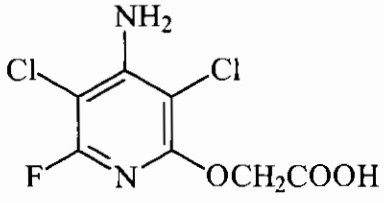
Fluroxypyr **(8)** was synthesised in a 4-stage reaction process according to the process outlined in the Agriguard bulletin and was analysed for impurities. It has been proposed that 6 impurities were present in technical fluroxypyr[49] as illustrated in figure 2.7.1.



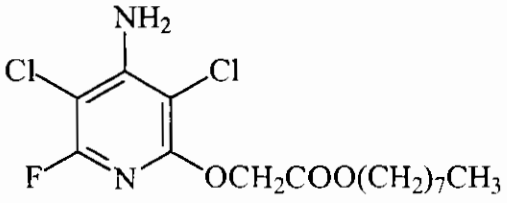
(18)



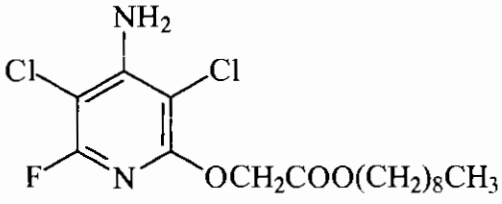
(73)



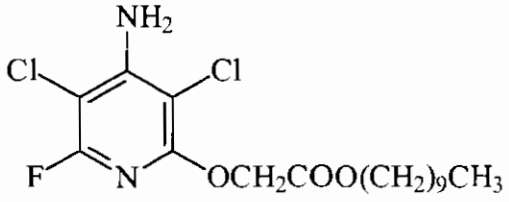
(78)



(79)



(80)



(81)

Figure 2.7.1

One of these impurities methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** was a reaction intermediate. A commercial standard was readily available for (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetic acid **(78)** so it was not necessary to synthesise it. The impurity 4-amino-3,5-dichloro-6-fluoro-2-methoxy pyridine **(18)** is the product of microbiological degradation of fluroxypyr **(8)**[24]. The impurities 1-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(79)**, 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(80)**, 1-decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(81)** are thought to arise from impurities present in 2-octanol **(74)** and are not commercially available. These compounds were prepared, in order to determine if they were present in the technical fluroxypyr and they

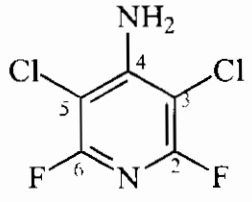
were characterised using ^{1}H NMR, ^{13}C NMR, infrared spectroscopy, GC-MS, melting points and elemental analysis. Once all the impurities were prepared, a theorctical technical fluroxypr was formulated and was compared by HPLC analysis to the technical fluroxypyr.

2.8 HPLC analysis of technical fluroxypyr (8)

Technical fluroxypyr **(8)** was analysed for reported impurities using HPLC. From the batches of technical fluroxypyr **(8)** analysed, it was found that all batches contained methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** between 0.03-0.1% and (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetic acid **(78)** between 0.04-0.1%. 1-Nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(80)** was found to be present in 2 out of 5 batches at a level of below 0.2%. 1-Decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(81)** was found to be present (0.1%) in 1 out of 5 of the batches tested. It was also found that 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine **(18)** and 1-octyl (4-amino-3,5,-dichloro-6-fluoro-2-pyridinyloxy) acetate **(79)** were not present in any of the batches analysed.

2.9 Synthesis of 4-amino-3,5-dichloro-2,6-difluoropyridine (70) from 3,5-dichloro-2,4,6-trifluoropyrine (69).

4-Amino-3,5-dichloro-2,6-fluoropyridine **(70)** was prepared by the ammonation of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** as described in section 2.3. After ammonation the 4-Amino-3,5-dichloro-2,6-fluoropyridine (**70**) was isolated by filtration. It was recyrstallised from petroleum ether 40-60^{O}C, melting point 112.2-114.2^{O}C (lit 112-114[50]). Spectral analysis of **(70)** showed peaks in the infrared spectra at 3488cm^{-1} (NH_2), 1600-1430cm^{-1} (C=C, C=N ring stretching skelatal bonding), 1055cm^{-1} (C-F), 788cm^{-1} (C-Cl). The ^{1}HNMR (200MHz, $CDCl_3$) showed a broad peak at δ 5.438ppm (NH_2). The ^{13}CNMR was complicated by the presence of two fluorine atoms attached to the ring, as each fluorine atom caused a n+1 splitting of each carbon signal. The peaks and coupling constant were as follows: δ_c (50MHz, $CDCl_3$) 155.0ppm (dd, C_2, C_6) JC_2-F_2/ C_6-F6 238Hz, JC_2-F_6/ C_6-F_2 18Hz, 151.939ppm (t, C_4) JC_4-F_2/ C_4-F6 5.6Hz, 96.864ppm ('inverted triplet**', C_3, C_5) JC_3-F_2 + C_3-F_6/ C_5-F_2 + C_5-F_6 40.6Hz (this corresponds to the separation of the outer members of the triplet)[51], (figure 2.9.1). ** The outer members of the triplet were more intense than the central one, giving the 'inverted triplet'.

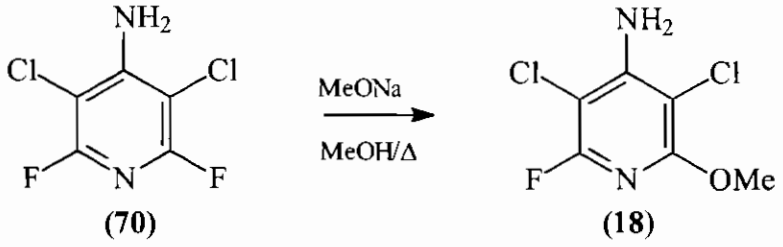


(70)

Figure 2.9.1

2.10 Synthesis of 4-amino-3,5-dichloro-5-fluoro-2-methoxypyridine (18) from 4-amino-3,5-dichloro-2,6-difluoropyridine (70).

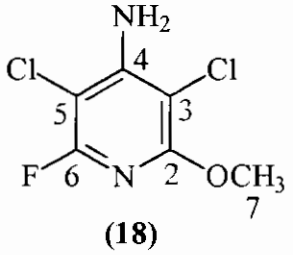
4-Amino-3,5-dichloro-6-fluoro-2-methoxy pyridine **(18)** was prepared by the reaction of 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** with sodium methoxide in methanol as illustrated in scheme 30



(70) **(18)**

Scheme 30

The precipitated product was collected by filtration and recyrstallised from petroleum ether 60-80°C yielding 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine **(18)** (64%), with a melting point of 106.5 –107°C (lit. melting point = 107.9-108.3°C)[52]. Spectral analysis revealed the presence of a CH stretching band at 2964cm^{-1} and the presence of C-O band at 1193cm^{-1} in the infrared spectrum. The ^{1}H NMR spectrum had the expected integration of 2:3 with the following peaks at 5.129ppm (broad, 2H, NH_2), 3.947ppm (s, 3H, CH_3). In the ^{13}C NMR a change in the splitting of the carbon lines in going from 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** to 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine **(18)** was observed. The peaks and coupling constants were as follows: δ (50MHz; $CDCl_3$) 156.094ppm (d, C_2) JC_2-F_6 17Hz, 155.658ppm (d, C_6) JC_6-F_6 233Hz, 150.146ppm (d, C_4) JC_4-F_6 5.3Hz, 96.802ppm (d, C_3) JC_3-F_6 5.3Hz, 93.141ppm (d, C_5) JC_5-F_6 38.5Hz, 54.732ppm ($O\underline{C}H_3$, C_7) (figure 2.10.1).

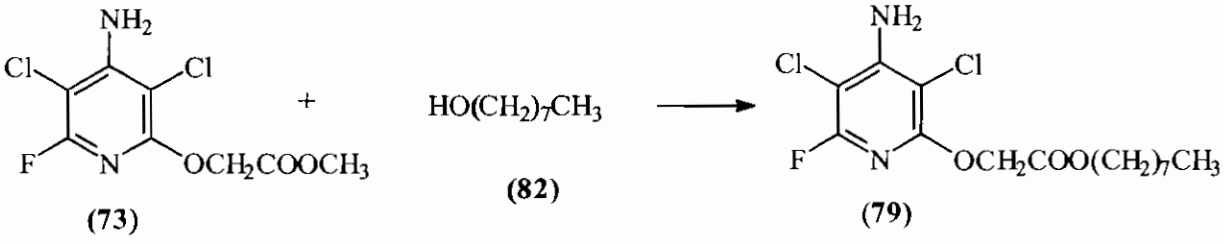


(18)

Figure 2.10.1

2.11 Synthesis of 1-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate(79) from methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate(73).

1-Octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(79)** was prepared by transesterification of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** with 1-octanol **(82)** as illustrated in scheme 31.



Scheme 31

The experimental procedure followed was an adaptation of the procedure used for the synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)**. The product yield was 79% before recrystallisation. The product **(79)** was recrystallised from petroleum ether 40-60°C and had a melting point of 70-70.5°C. Infrared analysis showed a broad carbonyl stretching band at 1748cm^{-1}. The ^{1}HNMR spectrum consisted of the following peaks at δ_H(200MHz; $CDCl_3$): 5.186ppm (broad, 2H, NH_2), 4.863ppm (s, 2H, CH_2-a), 4.157ppm (t, 2H, CH_2-b), 1.644ppm (m, 2H, CH_2-c), 1.251ppm (s, 10H, $(CH_2)_5$-d,e,f,g,h), 0.868ppm (s*, 3H, CH_3-i) (figure 2.11.1).

* A singlet was observed for this methyl group however a triplet was expected and may appear at higher resolution. This phenomena was also observed in compounds **(80)** and **(81)**.

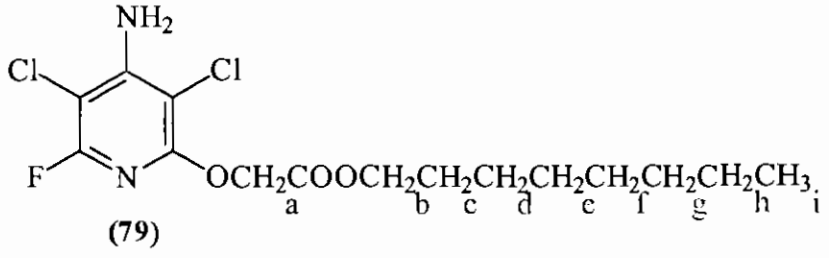
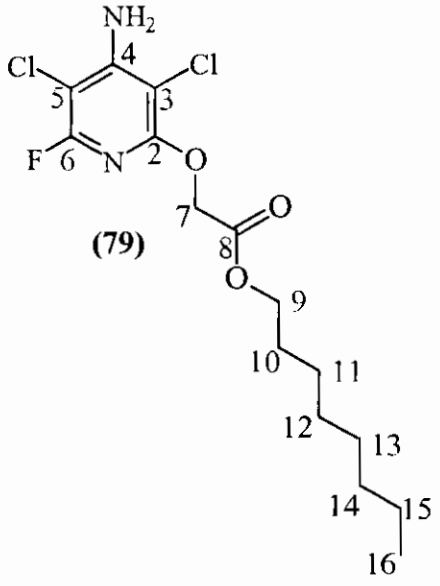


Figure 2.11.1

The ^{13}CNMR spectrum showed peaks at δ_C (50MHz; $CDCl_3$): 168.467ppm (C=O, C_8), 155.282ppm (d, C_6) JC_6-F_6 234.9Hz, 154.516ppm (d, C_2) JC_2-F_6 16.8Hz,

150.585ppm (d, C_4) JC_4-F_6 5.3Hz, 96.92ppm (d, C_3) JC_3-F_6 5.7Hz, 93.866ppm (d, C_5) JC_5-F_6 38Hz, 65.407ppm ($\underline{C}H_2$, C_7), 63.245ppm ($\underline{C}H_2$, C_9), 31.660ppm ($\underline{C}H_2$, C_{14}), 29.043ppm ($2\underline{C}H_2$ this peak was of greater intensity than others, C_{12}, C_{13}), 28.398ppm ($\underline{C}H_2$, C_{10}), 25.659ppm ($\underline{C}H_2$, C_{11}), 22.541ppm ($\underline{C}H_2$, C_{15}), 13.975ppm ($\underline{C}H_3$, C_{16}), (figure 2.11.2).



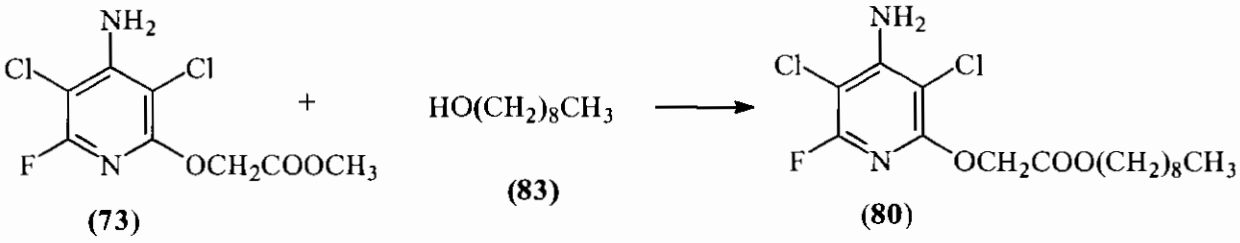
(79)

Figure 2.11.2

The ^{13}C NMR spectra were assigned on the basis of the ^{13}C calculated using Chem Windows.[53]

2.12 Synthesis of 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (80) from methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate(73)

1-Nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(80)** was prepared by transesterification of 1-nonanol **(83)** with methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)**, as shown in scheme 32.



Scheme 32

The experimental procedure followed was an adaptation of the procedure used for the synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8)** and the product yield was 85% before recrystallisation. The product **(80)** was recrystallised from petroleum ether 40-60°C and had a melting point of 66-67°C. The infrared spectrum showed a carbonyl stretching band at 1748cm^{-1}. The ^{1}H NMR spectra consisted of the following peaks δ_H (200MHz; $CDCl_3$): 5.179ppm (broad, 2H, NH_2), 4.865ppm (s, 2H, CH_2-a), 4.158ppm (t, 2H, CH_2-b), 1.620ppm (s, 2H, CH_2-c), 1.252ppm (s, 12H, $(CH_2)_6$-d,e,f,g,h,i), 0.871ppm (s, 3H, CH_3-j), (figure 2.12.1) .

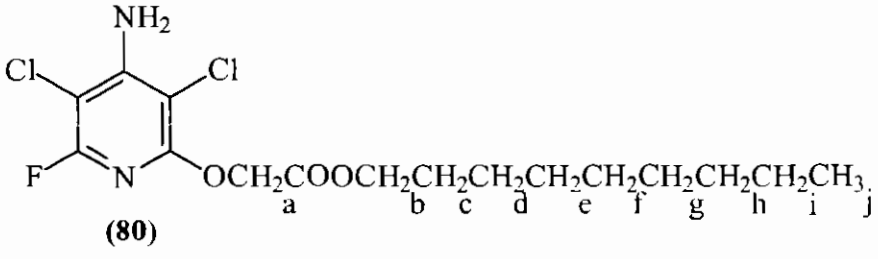


Figure 2.12.1

The peaks and coupling constant of 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(80)** in the ^{13}C NMR were as follows δ_C (50MHz; $CDCl_3$): 168.469ppm (C=O, C_8), 155.294ppm (d, C_6) JC_6-F_6 233Hz, 154.535ppm (d, C_2) JC_2-F_6 16Hz, 150.582ppm (d, C_4) JC_4-F_6 5.7Hz, 96.946ppm (d, C_3) JC_3-F_6 5.3Hz, 93.881ppm (d, C_5) JC_5-F_6 38Hz, 65.415ppm ($\underline{C}H_2$, C_7), 63.260ppm ($\underline{C}H_2$, C_9), 31.766ppm ($\underline{C}H_2$, C_{15}), 29.361ppm ($\underline{C}H_2$, C_{13}), 29.126ppm ($\underline{C}H_2$, C_{12}), 29.088ppm ($\underline{C}H_2$, C_{14}), 28.413ppm ($\underline{C}H_2$, C_{10}), 25.666ppm ($\underline{C}H_2$, C_{11}), 22.563ppm ($\underline{C}H_2$, C_{16}), 14.013ppm ($\underline{C}H_3$, C_{17}) (figure 2.12.2).

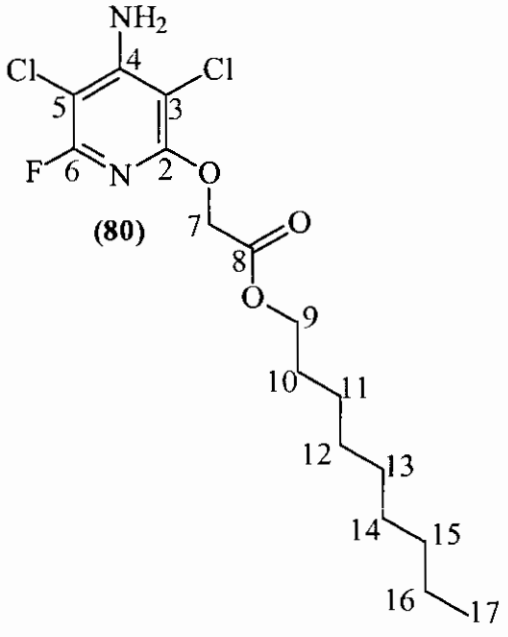
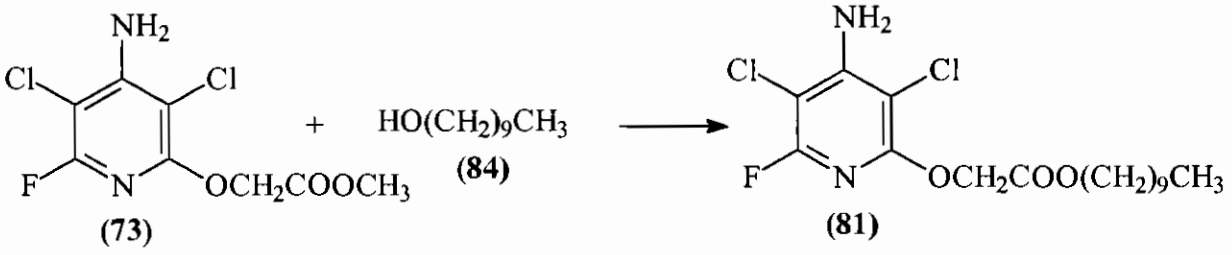


Figure 2.12.2

2.13 Synthesis of 1-decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (81) from methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73)

1-Decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (**81**) was prepared by transesterification of 1-decanol (**84**) with methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (**73**), as shown in scheme 33.



Scheme 33

The experimental procedure followed was an adaptation of the procedure used for the synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (**8**). The product yield was 54%, before recrystallisation. The product (**81**) was recrystallised from petroleum ether 40-60°C and had a melting point of 65-65.5°C. The infrared spectra showed a carbonyl stretching band at 1748cm^{-1}. ^{1}H NMR consisted of the following peaks δ_H (200MHz; $CDCl_3$): 5.174ppm (b, 2H, NH_2), 4.868ppm (s, 2H, CH_2, a), 4.159ppm (t, 2H, CH_2, b), 1.601ppm (t, 2H, CH_2, c), 1.252ppm (s, 14H, $(CH_2)_7$ d, e, f, g, h, i, j), 0.872ppm (s, 3H, CH_3 k,), (figure 2.13.1).

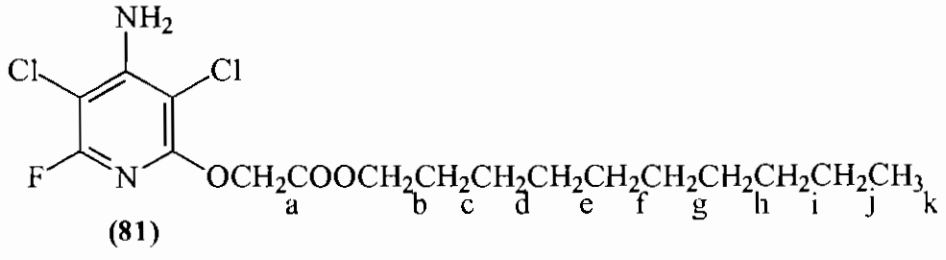
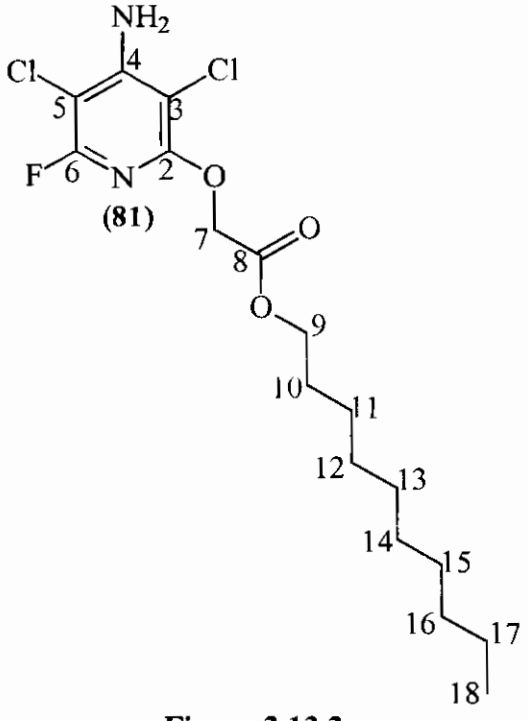


Figure 2.13.1

The ^{13}C NMR spectrum showed peaks at δ_C (50MHz; $CDCl_3$): 168.454ppm (C=O, C_8), 155.287ppm (d, C_6) JC_6-F_6 234Hz, 154.532ppm (d, C_2) JC_2-F_6 16.8Hz, 150.552ppm (d, C_4) JC_4-F_6 5.7Hz, 96.947ppm (d, C_3) JC_3-F_6 5.3Hz, 93.885ppm(d, C_5) JC_5-F_6 38Hz, 65.40ppm ($\underline{C}H_2$, C_7), 63.26ppm ($\underline{C}H_2$, C_9), 28.398ppm ($\underline{C}H_2$, C_{10}), 25.659ppm ($\underline{C}H_2$, C_{11}), 29.415ppm ($\underline{C}H_2$, C_{12}), 29.089ppm ($\underline{C}H_2$, C_{13}), 29.218ppm ($\underline{C}H_2$, C_{14}), 29.415ppm ($\underline{C}H_2$, C_{15}), 31.79ppm ($\underline{C}H_2$, C_{16}), 22.587ppm ($\underline{C}H_2$, C_{17}), 14.021ppm ($\underline{C}H_3$, C_{18}) (figure 2.13.2).



(81)

Figure 2.13.2

2.14 GC-MS analysis of fluroxypyr (8) and some of the impurities reported to be formed.

The molecular weights of impurities methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73),** 1-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(79),** 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(80)** and 1-decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(81),** were obtained using a "soft ionisation" technique; chemical ionisation (CI). The molecular ions were identified from the $(M+1)^{+\bullet}$ ions using the CI technique. This method was used, as some of the compounds did not exhibit molecular ions using the electron ionisation (EI) technique.

All of the compounds in question contain two chlorine atoms. Chlorine consists of two isotopes ^{35}Cl (75.8% natural abundance) and ^{37}Cl (24.2% natural abundance). The presence of chlorine atoms creates a dramatic effect in the mass spectrum, for ions containing one chlorine atom the relative intensities of the ions, separated by two mass units, is 3:1. For each element in a given ion, the relative contribution to m + 1 and m + 2 peaks etc. can be calculated from the binomial expansion of $(a + b)^n$, where a and b are the relative abundance of the isotopes and n the number of these atoms present in the ion. Thus for two chlorine atoms in an ion, expansion gives $a^2 + 2ab + b^2$. Since the relative abundances of ^{35}Cl and ^{37}Cl are 3:1, the intensities of the three peaks are 9:6:1 separated by two mass units at M, M + 2 and M + 4.

Fragmentation of esters of aromatic acids.

The molecular ion peak of methyl esters of aromatic acids is prominent. As the size of the alcohol moiety increases, the intensity of the molecular ion peak decreases rapidly to practically zero with a chain length of five carbons or more. The base peak can result from elimination of ·OR or the elimination of ·COOR. In the methyl ester these are present at M – 31 and M –59 respectively.

As the alkyl moiety increase in length 3 modes of cleavage become important,

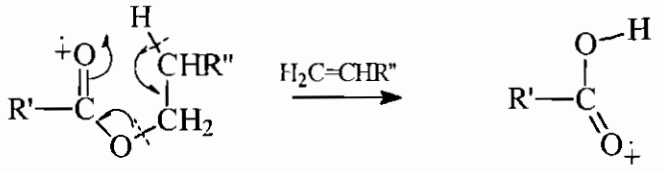
(1) Mclafferty rearrangement as illustrated in scheme 34

(2) Rearrangement of two H atoms with elimination of an allylic radical, as illustrated in scheme 35

(3) Retention of the positive charge by the alkyl group as illustrated in scheme 36

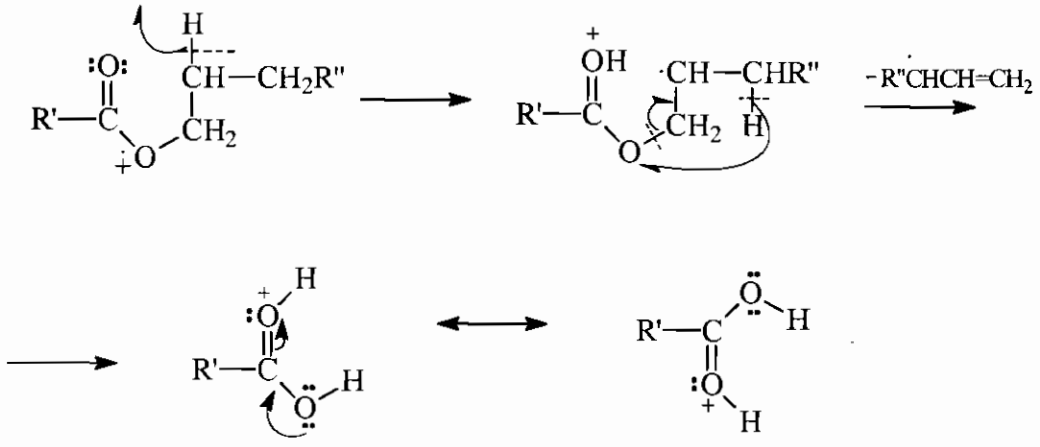
In the compounds in question these rearrangements lead to peaks at m/z 244 and 245.

1)



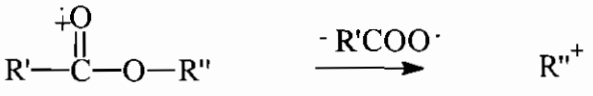
Scheme 34

2)



Scheme 35

3)



Scheme 36

The breakdown of impurities **(73), (79), (80)** and **(81)** is illustrated in the type of fragmentation pattern shown in figure 2.14.1.

The base peak for compound **(73)** was the molecular ion peak at 268. The ion at 237 resulted from the loss of a $CH_3O\bullet$ radical from the molecular ion and the prominent peak at 209 was due to the loss of the $\bullet COOCH_3$ radical from the molecular ion.

Compounds **(79), (80)** and **(81)** were found to have molecular weights of 269, 381 and 395 respectively, obtained using the CI technique. The breakdown of each shows the typical fragmentation of long chain esters of aromatic acids. The peak at 209 results from the loss of the •COOR radical, the peak at 237 is due to the loss of the OR

radical from the molecular ion. The peak at 254, 255 are due to the molecule undergoing one of the rearrangements which have already been discussed for esters of aromatic esters. The peak at 181 results from the loss of the side chain from the 2-position on the pyridine ring.

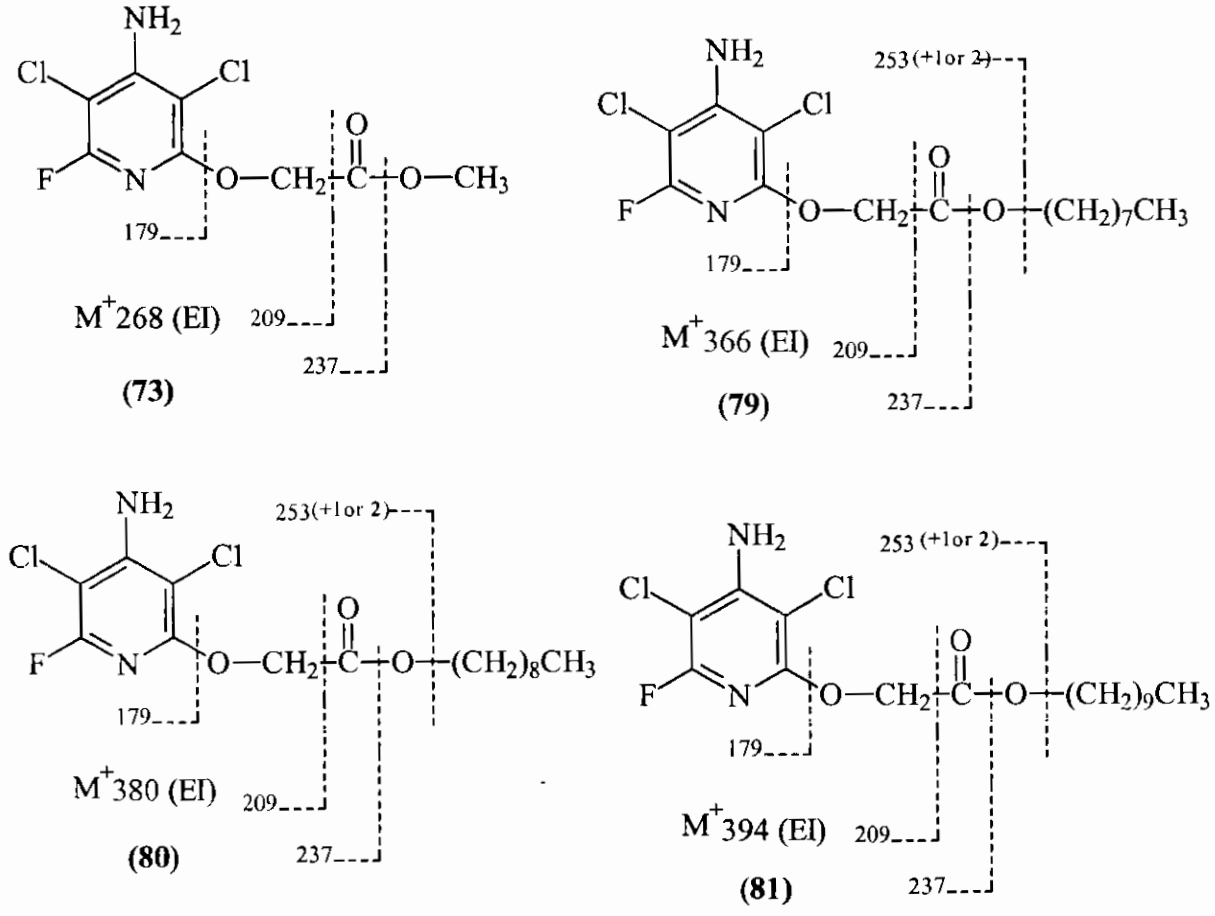
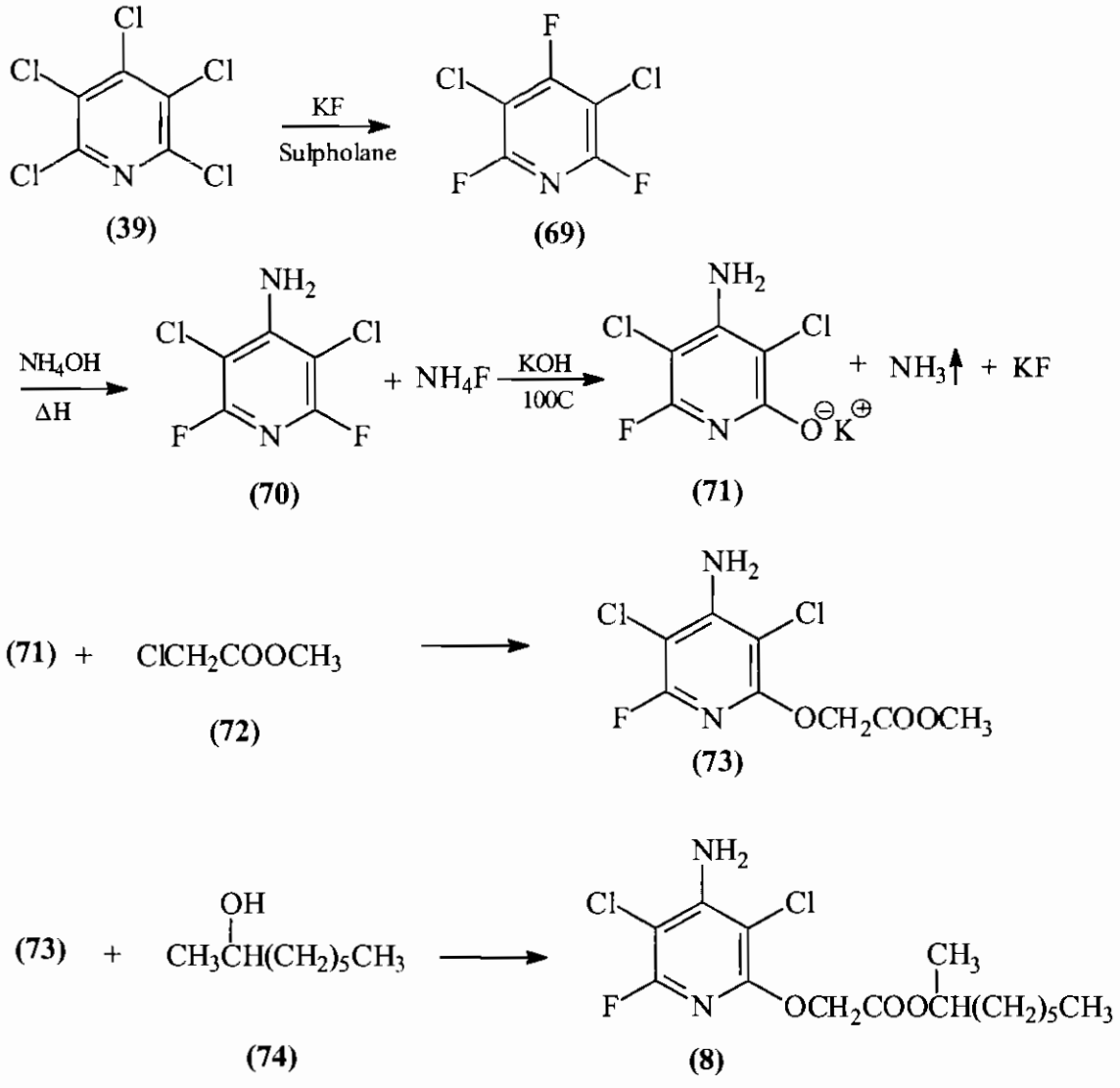


Figure 2.14.1

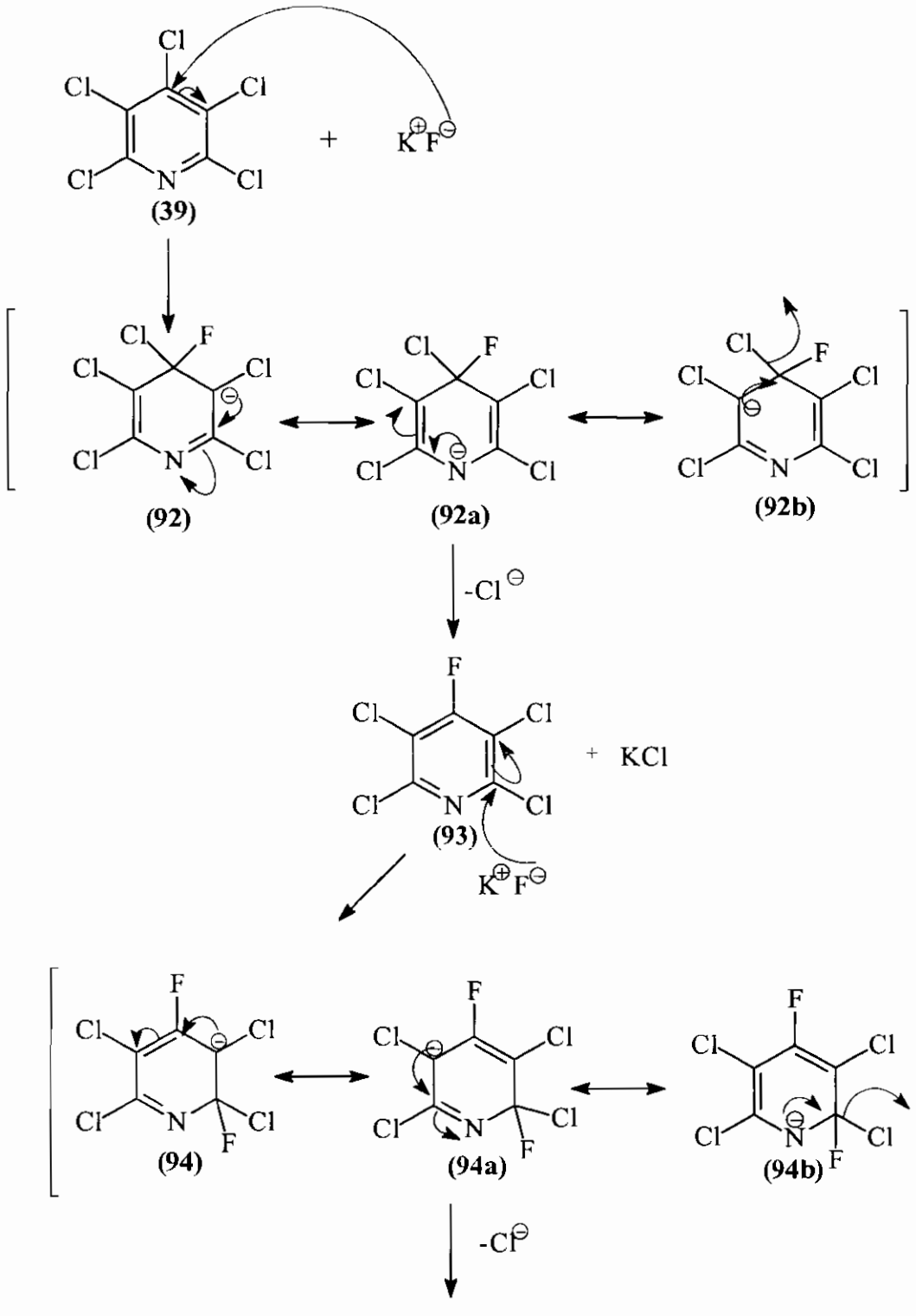
2.15 Mechanisms

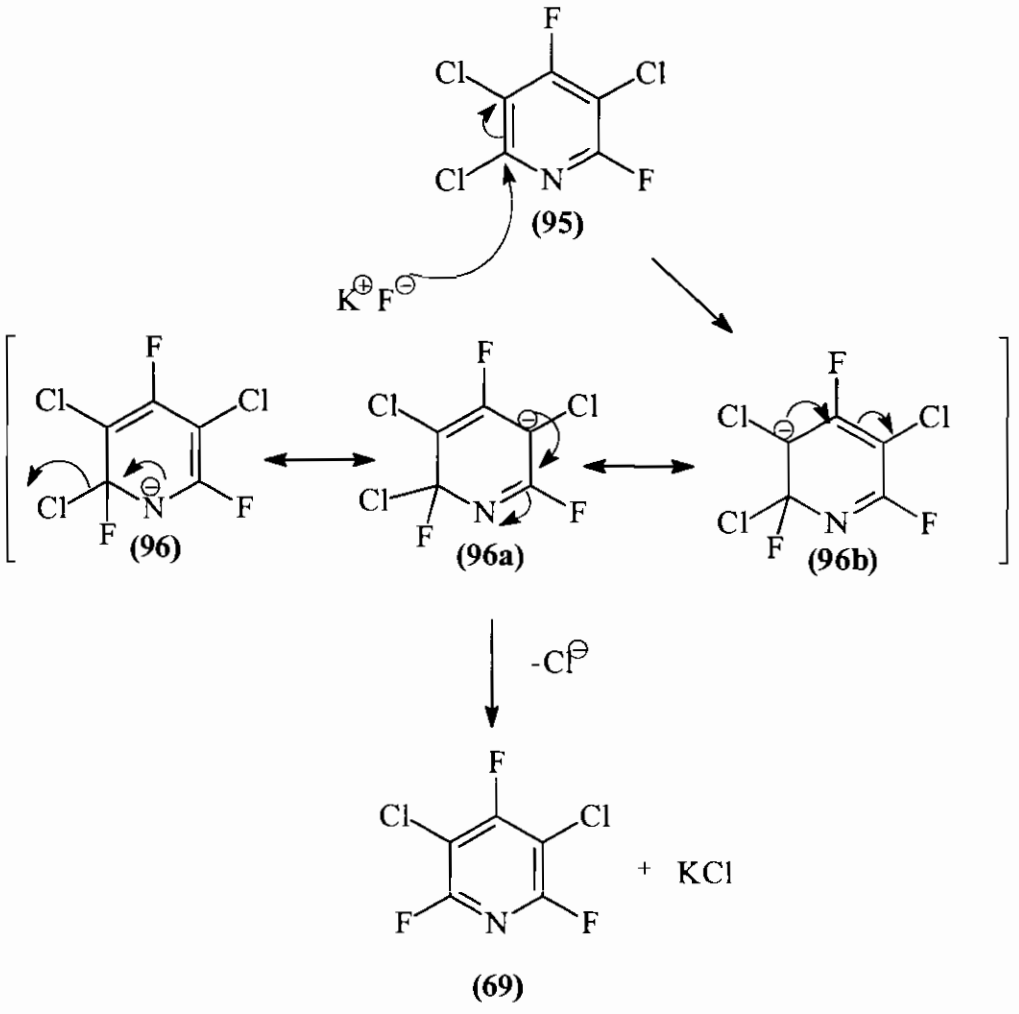
The synthesis of fluroxypyr **(8)** was achieved as shown in reaction scheme 22.



Scheme 22

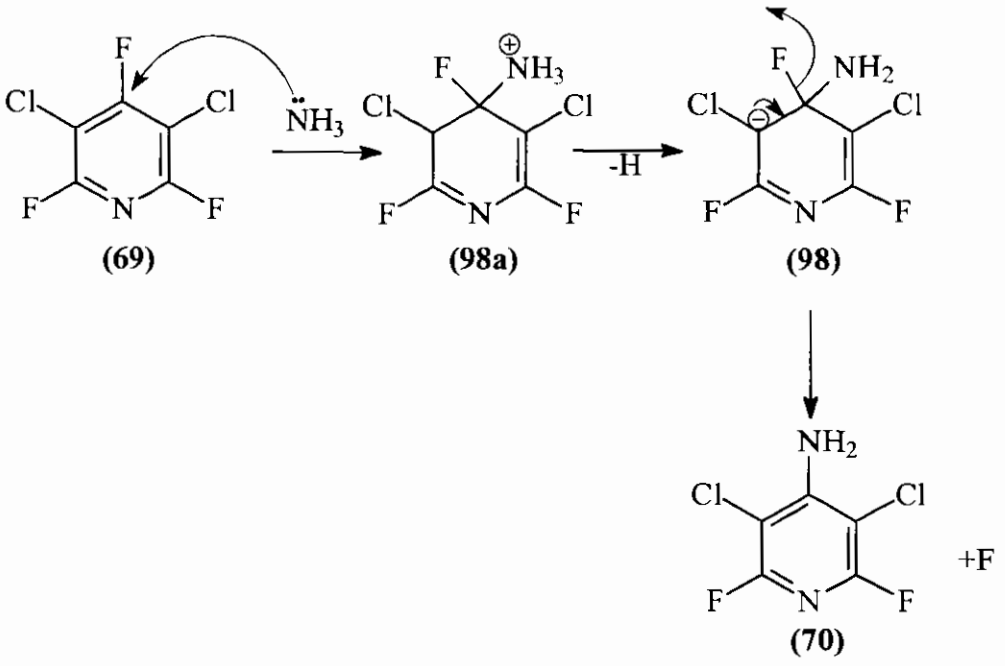
The first step was the conversion of pentachloropyridine **(39)** to 3,5-dichloro-2,4,6-trifluoropyridine **(69)** via a nucleophilic substitution mechanism. Halopyridines react with nucleophiles by an addition elimination mechanism (AE). AE reactions of pyridines occur most easily at the 2-, 4- and 6- position. When attack at 2, 4 and 6 positions occurs, stable intermediate anions are formed (where the partial charge resides on the electronegative nitrogen) as illustrated in scheme 7. In this reaction the fluoride ion from potassium fluoride attacks the pyridine ring at the 2-, 4- and 6- positions as shown in scheme 37. The reaction was controlled by heating the reaction mixture for 30 minutes.


Cl
Cl
Cl
Cl
N
Cl
(39)
+
K⊕F⊖
Cl
F
Cl
Cl
Cl
N
Cl
(92)
Cl
F
Cl
Cl
Cl
N
Cl
(92a)
Cl
F
Cl
Cl
Cl
N
Cl
(92b)
-Cl⊖
F
Cl
Cl
Cl
N
Cl
(93)
+ KCl
K⊕F⊖
F
Cl
Cl
Cl
N
Cl
F
(94)
F
Cl
Cl
Cl
N
Cl
F
(94a)
F
Cl
Cl
Cl
N
Cl
F
(94b)
-Cl⊖



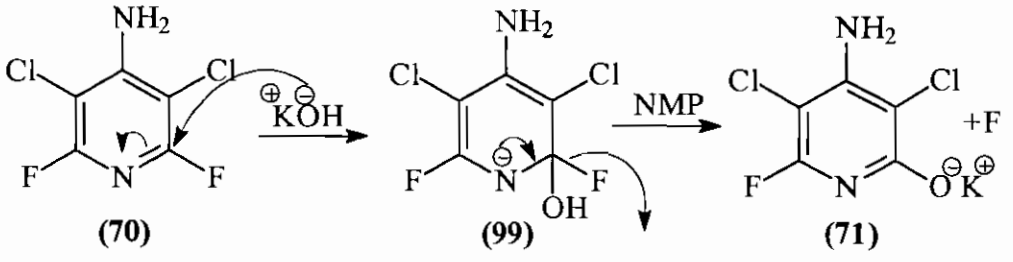
Scheme 37

The second step involves the conversion of 3,5-dichloro-2,4,6-trifluoropyridine **(69)** to 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** by reaction with aqueous ammonia as shown in scheme 38. This was a nucleophilic substitution reaction, where NH_2^- is a stronger nucleophile than fluorine. Pentafluoropyridine **(97)** undergoes substitution only at the 4- position in reactions with amines[54]. Therefore it was proposed that 3,5-dichloro-2,4,6-trifluoropyridine **(69)** would undergo substitution only at the 4- position. This was confirmed by examining the coupling constants in the ^{13}C NMR.



Scheme 38

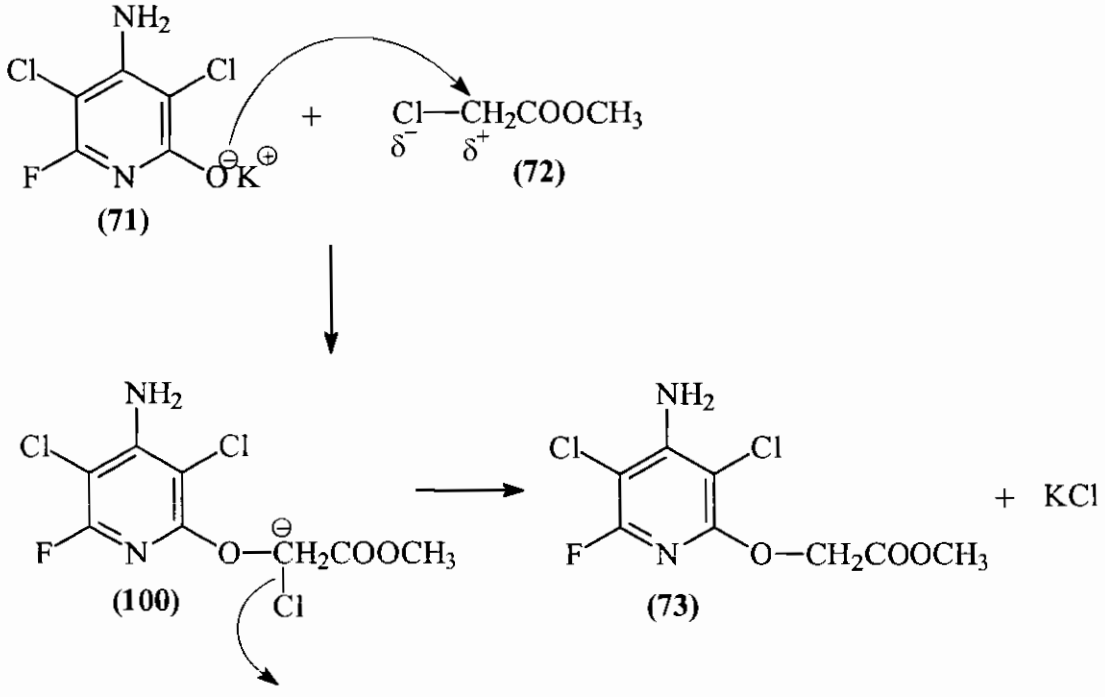
Potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** was prepared by the base hydrolysis of 4-amino-3,5-dichloro-2,6-difluoropyridine **(70).** This was achieved by reacting 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** with aqueous potassium hydroxide. The fluoride in the 2- position was displaced by the ^{-}OH ion by an addition elimination reaction mechanism as shown in scheme 39. The addition of NMP **(75)** and then the concentration of the water layer causes the precipitation of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71).**



Scheme 39

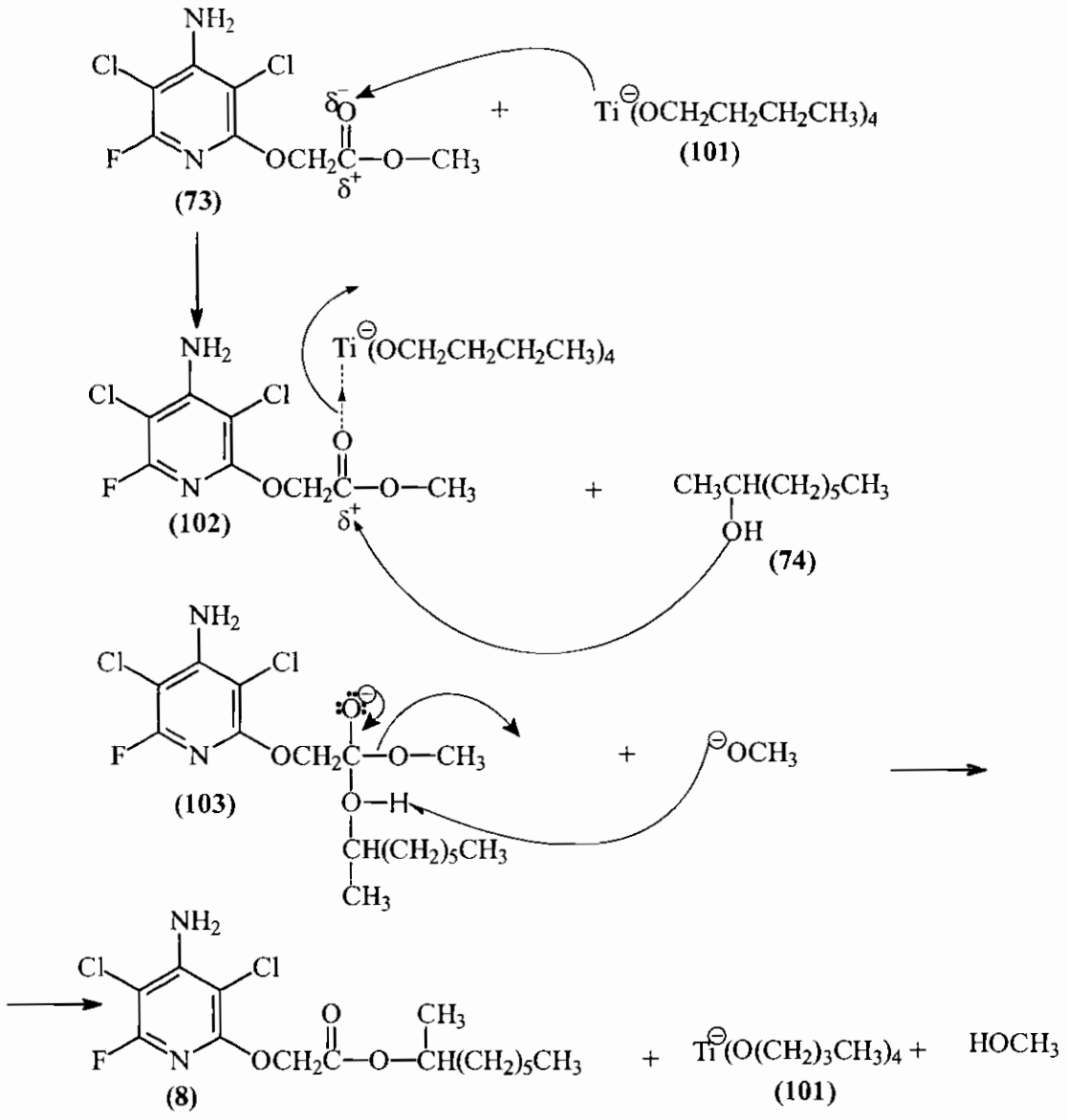
The next stage of the synthesis involves the conversion of potassium 4-amino-3,5-dichloro-6-fuoro-2-pyridinate **(71)** to methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate**(73).** This is a Williamson type reaction and is the best general method for the preparation of unsymmetrical ethers. The reaction was brought about by reacting **(71)** with methyl chloroacetate **(72)** in NMP **(75).** The use of an aprotic dipolar

solvent (NMP **75**) assists in the ionisation of the oxygen and promotes O-alkylation, as shown in scheme 40. This is an SN2 type reaction, where potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate **(71)** attacks **(72)** to form the transition state **(100)** the chloride ion is lost to form methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** as shown in scheme 40.



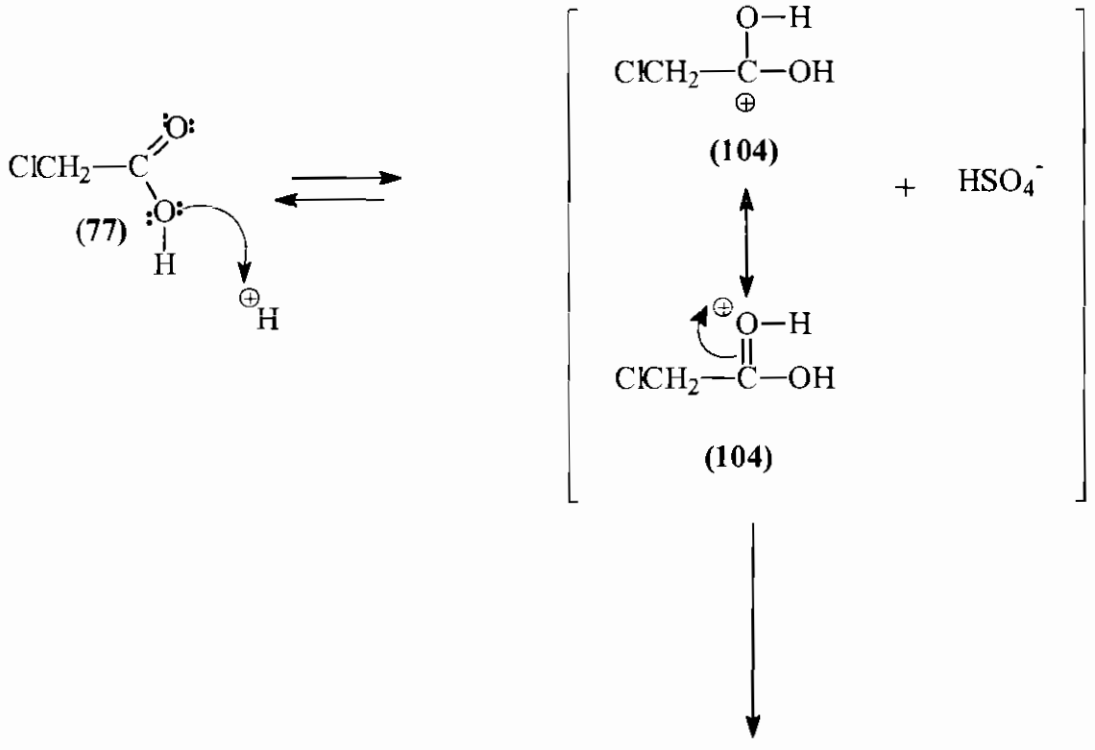
Scheme 40

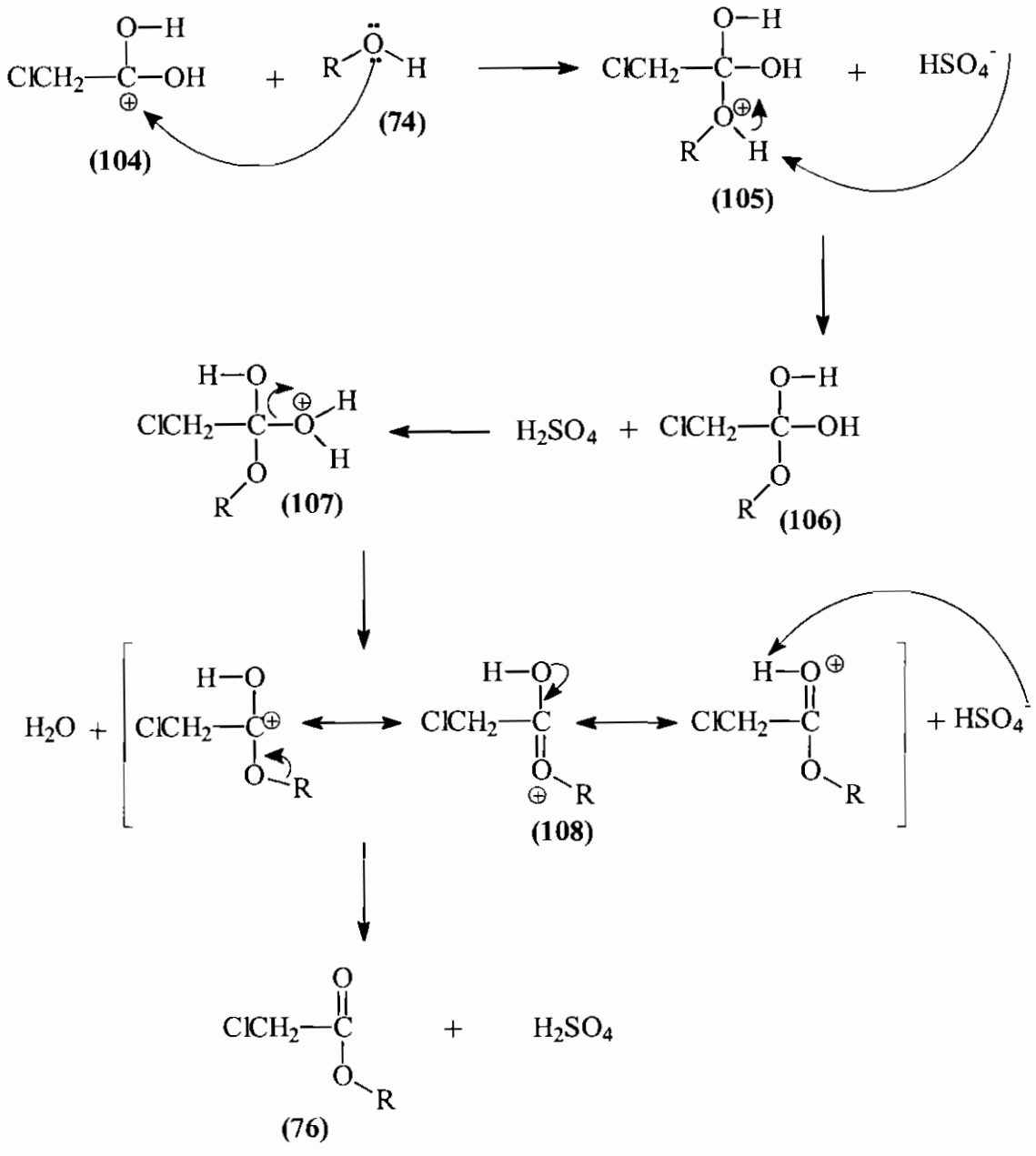
In the final stage methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(73)** was reacted with 2-octanol **(74)** in the presence of titanium (IV) butoxide catalyst **(101)** to yield 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8).** This was a base catalysed reaction, the alcohol (2-octanol **(74)**) was first deprotonated by the butoxide ion (from the catalyst) and the resulting alkoxide ion (1-methylheptyloxide ion **(74a))** then attacks the carbonyl group to form the intermediate **(102),** which loses methoxide to form 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(8).** The methoxide ion was then protonated to form methanol and the catalyst was regenerated, as shown in scheme 41.


NH2
Cl
Cl
F
N
OCH2C—O—CH3
(73)
+
Ti⊖(OCH2CH2CH2CH3)4
(101)
(102)
CH3CH(CH2)5CH3
OH
(74)
(103)
OCH3
CH(CH2)5CH3
CH3
(8)
HOCH3

Scheme 41

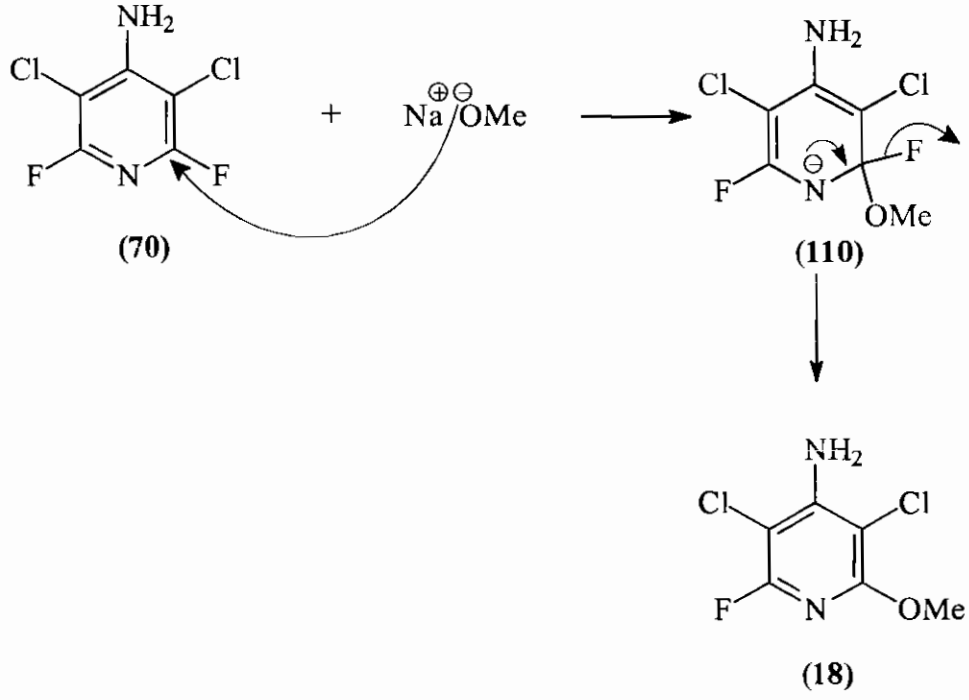
The alternative route for the synthesis of fluoroxypyr **(8)** follows a similar mechanism as that shown in scheme 40. 1-Methylheptyl chloroacetate **(76)** was formed by acid catalysed esterification of chloroacetic acid **(77)** with 2-octanol **(74)** and was catalysed by sulphuric acid, as shown in scheme 42. Esterification occurs when a proton (from sulphuric acid) adds to the carbonyl group of chloroacetic acid **(77)** to form a carbocation intermediate **(104),** which was then open to attack by 2-octanol **(74)**. The lone pairs of electrons on the oxygen are donated to the positive carbon to form the intermediate **(105)**. Which loses a proton to form the intermediate **(106)** with the regeneration of sulphuric acid. The carbonyl hydroxyl group is then protonated to give the intermediate **(107)**, which loses water to form a new intermediate **(108)** which rearranges to give 1-methylheptyl chloroacetate **(76)** and sulphuric acid.





Scheme 42

The impurities 1-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(79)**, 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(80)**, 1-decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate **(81)** are formed by an analogous mechanisms to that shown in scheme 38. The impurity 4-amino-3,5-dichloro-5-fluoro-2-methoxypyridine **(18)** was formed by reacting 4-amino-3,5-dichloro-2,6-difluoropyridine **(70)** with sodium methoxide in methanol as shown in scheme 43. This was a nucleophilic substitution reaction where the methoxide ion replaces the fluoride ion in the 2- position, this occurred as the methoxide ion is a stronger nucleophile than the fluoride ion.



Scheme 43

Chapter 3
Experimental

3.0 Experimental

NMR spectra were determined using a Varian Gemini^{TM} 200MHz spectrometer equipped with Solarius^{TM} software, using deuterated chloroform and deuterated dimethylsulphoxide. The infrared spectra, as KBr discs and neat samples were recorded using a Perkin Elmer spectrometer. GC-MS spectra were obtained on a Varian Star 3400CX^{TM} gas chromatograph coupled to a Varian Star 2000^{TM} mass spectrometer. The column used in GC was a DB5 (30 meters lenght, 0.25mm diameter, film coating 25microns) capillary column. GC parameters involved 80°C for 2 minutes followed by increase to 290°C at 20°C per minute, held at 290°C for 12.5 minutes, total run time 25 minutes. MS parameters: Mass range 40-450 m/z for EI and 70-450 m/z for CI, scans 1 per second, segment length 25 minutes, filament delay 3 minutes

HPLC monitoring of reactions were carried out using a Shimadzu LC-6A connected to a Waters UV detector (254nm), the column used was a hypersil 5μm ODS (C_{18}) 250 by 4.6mm, mobile phase used was 80:20:0.04 precent MeCN: H_2O: H_3PO_4 at a flow rate of 1.2ml per minute. HPLC analysis was obtained using Varian 9002 (isogratic pump) and a variable UV detector Varian 9050.

3.1 Synthesis of 3,5-dichloro-2,4,6-trifluoropyridine

Tetramethylene sulphone (150.0 g) was added to a reaction flask (500cm^3) fitted with a flange lid, mechanical stirrer, thermometer and condenser. Potassium fluoride (57.0 g, 0.98 moles) was added when the reaction temperature reached 100°C and pentachloropyridine (50.0 g, 0.20moles) was added when the reaction temperature reached 150°C. The reaction was refluxed at 210°C for 30 minutes. The reaction mixture was distilled under reduced pressure to yield a clear liquid which solidified on cooling to yield colourless crystals of 3,5-dichloro-2,4,6-trifluoropyridine, (30.1g, 0.15 moles, 75.3%), bpt. 29°C 1.5 mbar (lit bpt. 159-160°C[40]), ν max., 1600-1430cm^{-1} (C=C, C=N ring stretching sheletal bands), 1055 cm^{-1} (C-F), 788cm^{-1} (C-Cl).

^{13}C NMR spectra: δ_c (50MHz; $CDCl_3$): 164.252ppm (C_4), 155.256ppm (C_2, C_6), 103.907ppm (C_3, C_5).

3.2 Synthesis of potassium 4-amino-3,5-dichloro-6-flouro–2-pyridinate

3,5-Dichloro-2,4,6-trifluoropyridine (27.25g, 0.136 moles) was added to a reaction flask (500cm^3), fitted with a flange lid, condenser, thermometer, dropping funnel and mechanical stirrer. Water (27.6g, 1.53moles) was added to the reaction flask and the resulting solution heated to 45°C. Aqueous ammonium hydroxide (35%, 22.3g) was added dropwise with stirring over 25 minutes with cooling to maintain the temperature below 50°C and then the mixture was kept at 45°C for one hour. The mixture was then heated to 60°C for one hour and the temperature was then increased to 100°C for 30 minutes. Potassium hydroxide solution (52%, 15.6g) was added and the reaction mixture was heated at 100°C for two hours. A further quantity of potassium hydroxide solution (52%, 28.07g) was then added dropwise and kept at 100°C for 2 hours (monitored using HPLC). The reaction mixture was then cooled and N- methyl-2-pyrrolidinone (87.8g, 0.886moles) was then added. The mixture was distilled under reduced pressure until a distillate (48g water) was obtained. N-methyl-2-pyrrolidinone (57.5g, 0.58moles) was added to the reaction mixture and a further quantity of water (20g, 1.11moles) was removed by distillation. The reaction mixture was heated to 80°C and then left to cool. An off-white solid precipitated. The supernatant brown liquid (containing the product) was decanted off and the solid (potassium fluoride dihydrate) removed. This was then used without isolation for step 3.

A sample isolated by the removal of solvent for spectral analysis showed ^{1}H NMR spectra δ_H (200MHz, d-DMSO): 5.254ppm (NH_2), ^{13}C NMR δ_c(50MHz, d-DMSO): 163.192ppm (d, C_2), 156.159ppm (d, C_6), 148.162ppm (d, C_4), 97.315ppm (d, C_3), 78.939ppm (d, C_5).

3.3 Synthesis of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate in N-methyl-2-pyrrolidinone

Potassium-4-amino-3,5-dichloro-6-fluoro-2-pyridinate solution (0.1349moles, based on a 99% conversion of 3,5-dichloro-2,4,6-trifluoropyridine as seen from HPLC) from step 2 was added to a reaction flask fitted with a thermometer, condenser, stirrer and dropping funnel. This was set-up for distillation to remove any volatiles. The mixture was heated to about 40-45°C with stirring and methyl chloroacetate (16.08g, 0.149moles) was added along with N-methyl-2-pyrrolidinone (17.4g, 0.176moles). The reaction was heated for 2 hours and monitored using HPLC. The excess methyl chloroacetate and other volatiles (5.4g) were distilled off. Water (89g) was added with stirring at about 80°C and after cooling, the solid that formed was collected by filtration and dried to yield an off white solid methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate, (29.03g, 0.108moles, 80%), mpt. 124.5-125.5°C. ν max.(KBr), 3485cm^{-1} (NH_2), 2954cm^{-1} (CH_3), 1755cm^{-1} (C=O), 1622-1410cm^{-1} (C=C, C=N ring stretching skeletal bands), 1082cm^{-1} (C-F), 788cm^{-1} (C-Cl). ^{1}H NMR spectra δ_H (200MHz $CDCl_3$): 5.196ppm (broad, 2H, NH_2), 4.877ppm (s, 2H, -OCH_2), 3.758ppm (s, 3H, -$OOCH_3$). ^{13}C NMR δ_C (50MHz, $CDCl_3$): 168.886ppm (C=O), 155.279ppm (C_6), 154.423 pm (C_2), 150.651ppm (C_4), 96.923ppm (C_3), 93.941ppm(C_5), 63.048ppm (-O$\underline{C}H_2$), 52.183ppm (-OO$\underline{C}H_3$). CIMS 269 m/z, EIMS 268 m/z. Analysis Found%: C, 35.39; H, 2.45; N, 10.28. Calculated for $C_8H_7N_2O_3Cl_2F$ %: C, 35.71; H, 2.62; N, 10.41.

3.4 Synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate.

A mixture of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (7.521g, 0.028moles) and water (0.7g, 0.039moles) was combined with 1-methylheptanol (13.5g, 0.104moles) in a $100cm^3$ 2-neck round bottom flask fitted with a thermometer, still head packed with beads, condenser, vacuum source and magnetic stirrer. The mixture was heated to 150°C and tetrabutyl titanate (catalytic amount) was added and the mixture was brought to reflux (180°C) while the methanol by-product was continuously removed (70°C, 0.7g, 0.023moles) by distillation. The reaction was monitored using HPLC and after two hours the excess 2-octanol was removed under vacuum (10.2g, 0.078moles) to yield a viscous liquid which solidified on cooling to yield 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate as a light grey solid (8.87g, 0.024moles, 89.26%), mpt. 55.0-56.4°C, Lit 56-57°C[48]). ν max., $3355cm^{-1}$ (NH_2), $2930cm^{-1}$ (CH), $1749cm^{-1}$ (C=O), $1627\text{-}1451cm^{-1}$ (C=C, C=N ring stretching skeletal bands), $1149cm^{-1}$ (C-F), $775cm^{-1}$ (C-Cl).

^1H NMR spectra δ_H (200MHz; $CDCl_3$): 5.210ppm (broad, NH_2), 4.983-4.953ppm (sextet, 1H, CH), 4.807ppm (s, 2H, CH_2), 1.548-1.475ppm (m, 2H, CH_2), 1.221-1.189ppm (m, 11H, $(CH_2)_4\ CH_3$), 0.875-0.813ppm (t, 3H, CH_3). ^{13}C NMR δ_C (50MHz; $CDCl_3$): 168.10ppm (C=O), 155.278ppm (C_6), 154.557ppm (C_2), 150.608ppm(C_4), 96.877ppm (C_3), 93.80ppm (C_5), 72.500ppm ($\underline{C}H_2$), 63.494ppm ($\underline{C}H$), 35.718ppm ($\underline{C}H_2$), 31.584ppm ($\underline{C}H_2$), 28.951ppm ($\underline{C}H_2$), 25.066ppm ($\underline{C}H_2$), 22.456ppm ($\underline{C}H_2$), 19.733ppm ($\underline{C}H_3$), 13.936ppm ($\underline{C}H_3$).

3.5 Synthesis of 1-methylheptyl chloroacetate

Chloroacetic acid (37.7g, 0.399moles), 2-octanol (86.4g, 0.664moles), sulphuric acid (2.6g, 0.027moles) and toluene (77.1g, 0.838moles) were added to a round bottom flask (250cm^3) fitted with a magnetic stirrer, dean and stark apparatus and condenser. The mixture was brought to reflux and continued refluxing until water (7.9g, 0.439moles) was removed. The reaction mixture was washed with water, sodium carbonate (5% solution) and water until a neutral pH was obtained. The mixture was then dried over anhydrous sodium sulphate and distilled to yield 1-methylheptyl chloroacetate (53.99g, 0.262moles, 65.55%), 92-93.5°C, 5mbar Hg, [lit. boiling 119-120°C 15mbar[55]]. ν max., 2940cm^{-1} (CH), 1745cm^{-1} (C=O), 781cm^{-1} (Cl-C). ^{1}H NMR δ_H (200MHz; $CDCl_3$): 4.909ppm (sextet, 1H, CH), 3.959ppm (s, 2H, CH_2), 1.505ppm (m, 2H, CH_2), 1.180ppm (m, 11H, $[CH_2]_4$, CH_3), 0.808ppm (t, 3H, CH_3). ^{13}C NMR δ_C (50MHz; $CDCl_3$): 166.801ppm (C=O), 73.253ppm (<u>C</u>H), 40.940ppm (<u>C</u>H_2), 35.493ppm (<u>C</u>H_2), 31.441ppm (<u>C</u>H_2), 28.786ppm (<u>C</u>H_2), 24.970ppm (<u>C</u>H_2), 22.291ppm (<u>C</u>H_2), 19.484ppm (<u>C</u>H_3), 13.741ppm (<u>C</u>H_3).

3.6 Alternative preparation of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate

Potassium (4-amino-3,5-dichloro-6-fluoro-2-pyridinate solution (0.05moles based on a 99% conversion of 3,5-dichlor-2,4,6-trifluoropyridine as seen form HPLC analysis) was placed in a 3-neck ($250cm^3$) round bottom flask fitted with a condenser, thermometer and magnetic stirrer. The mixture was heated to 45°C and methylheptyl chloroacetate (11.3g,) and N-methyl-2-pyrrolidone (30g,) was added. The reaction mixture was heated to 100°C for 30 minutes, and the volatiles were distilled off. Water (80g) was added with stirring to yield two layers. The bottom layer was recovered and the volatiles were distilled off (0.6mbar, 50-76°C) to yield a dark green oil which solidified on cooling (40-45°C). The crude solid was recrystallised from hexane to yield 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (7.52g, 0.02moles, 40.96%), melting point 55.9-56.9°C (lit. 56-57°C[48]).

3.7 Synthesis of 4-amino-3,5-dichloro-2,6-difluoropyridine

3,5-Dichloro-2,4,6-trifluoropyridine (25g, 0.124moles) and water (25.5g, 1.417moles) was added to a 250cm^3 round bottom flask fitted with a condenser, dropping funnel, and magnetic stirrer. The mixture was heated to 45°C. Aqueous ammonium hydroxide (35%, 27g, 0.559moles) was added dropwise with stirring and cooling to maintain the temperature below about 50°C and kept at 45°C for one hour and then heated to 60°C for one hour. The temperature was then increased to 100°C for 30 minutes. The mixture was then cooled. The resultant white solid was isolated by filtration to yield 4-amino-3,5-dichloro-2,6-difluoropyridine (20.8g, 0.105moles, yield 84.05%). This was recrystallised using petroleum ether (40-60°C) to form rod like crystals melting point 112.2-114.2°C, lit mpt 112-114°C[50] ν max., 3488cm^{-1} (NH_2), 1600-1430cm^{-1} (C=C, C=N ring stretching skeletal bands), 1055cm^{-1} (C-F), 788cm^{-1} (C-Cl).^{1}H NMR spectra: δ_H (200MHz; $CDCl_3$): 5.438ppm (broad, NH_2). ^{13}C NMR δ_C (50MHz; $CDCl_3$): 155.0ppm (C_2, C_6), 151.939ppm (C_4), 96.864ppm (C_3, C_5).

3.8 Synthesis of 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine

4-Amino-3,5-dichloro-2,6-difluoropyridine (10.2g, 0.057moles) was dissolved in methanol at room temperature in a 100cm^3 round bottom flask. A solution of sodium methoxide was prepared by dissolving sodium (1.154g, 0.05moles) in methanol (50cm^3) and this was added dropwise with stirring to the solution. The reaction mixture was then heated to reflux for 3 hours. The reaction mixture was cooled and then poured into excess distilled water. The precipitated product was collected by filtration and recrystallised from petroleum-ether (40-60°C) to yield 4-amino-3,5-dichloro-6-fluoro-2-methoxypyridine (6.967g, 0.03moles, 64.408%), melting point 106.5-107°C, (lit mpt. =107.9-108.3°C)[52] ν max., 3374cm^{-1} (NH_2), 2964cm^{-1} (CH), 1193cm^{-1} (C-O) 1616-1411cm^{-1} (C=C, C=N ring stretching skeletal bands), 1088cm^{-1} (C-F), 769cm^{-1} (C-Cl). ^{1}H NMR spectra: δ_H (200MHz; $CDCl_3$): 5.129ppm (broad, 2H, NH_2), 3.947ppm (s, 3H, CH_3). ^{13}C NMR δ_C (50MHz; $CDCl_3$): 156.094ppm (C_2), 155.658ppm (C_6), 150.146ppm (C_4), 96.802ppm (C_3), 93.141ppm (C_5), 54.732ppm ($O\underline{C}H_3$).

3.9 Synthesis of 1-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridnyloxy) acetate

A mixture of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (15.00g, 0.056moles) and water (0.7g, 0.039moles) was combined with 1-octanol (34.70g, 0.267moles) in a 100cm^3 2-neck round bottom flask fitted with a thermometer, still head packed with beads, condenser, vacuum source and magnetic stirrer. The mixture was heated to 150°C and tetrabutyl titanate (catalytic amount) was added and the mixture was brought to reflux (180°C). The methanol by-product was continuously removed (70°C, 1.4g, 0.047moles) by distillation. The reaction was monitored using HPLC and after two hours the excess 1-octanol was removed under vacuum (27.53, 0.211moles). This resulted in a viscous liquid which solidified on cooling to yield 1-octyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate which on recrystallisation from petroleum ether 40-60°C yielded white crystals (16.2g, 0.044moles, 79.24%), mpt. 70-70.5°C. ν max., 3360cm^{-1} (NH_2), 2925cm^{-1} (CH), 1748cm^{-1} (C=O), 1610-1444cm^{-1} (C=C, C=N ring stretching skeletal bands), 1153cm^{-1} (C-F), 763cm^{-1} (C-Cl). ^{1}H NMR spectra: δ_H (200MHz; $CDCl_3$): 5.186ppm (broad, 2H, NH_2), 4.863ppm (s, 2H, CH_2), 4.157ppm (t, 2H, CH_2), 1.629ppm (m, 2H, CH_2), 1.251ppm (s, 10H, $(CH_2)_5$), 0.868ppm (s, 3H, CH_3). ^{13}C NMR δ_C (50MHz; $CDCl_3$): 168.467ppm (C=O), 155.282ppm (C_6), 154.516ppm (C_2), 150.585ppm (C_4), 96.92ppm (C_3), 93.866ppm (C_5), 65.407ppm ($\underline{C}H_2$), 63.245ppm ($\underline{C}H_2$), 31.660ppm ($\underline{C}H_2$), 29.043ppm ($\underline{C}H_2$ X 2), 28.398ppm ($\underline{C}H_2$), 25.659ppm ($\underline{C}H_2$), 22.541ppm ($\underline{C}H_2$), 13.975ppm ($\underline{C}H_3$). CIMS 367 m/z. Analysis:Found%: C, 48.95; H, 5.56; N, 7.50. Calculated for $C_{15}H_{21}N_2O_3Cl_2F$%: C, 49.06; H, 5.76; N, 7.62.

3.10 Synthesis of 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate

A mixture of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (10.0g, 0.037 moles) and water (0.7g, 0.039 moles) was combined with 1-nonanol (25g, 0.173 moles) in a $100cm^3$ 2-neck round bottom flask fitted with a thermometer, still head packed with beads, condenser, vacuum source and magnetic stirrer the mixture was heated to 150°C and tetrabutyl titanate (catalytic amount) was added and the mixture was then brought to reflux (180°C). The methanol by-product was continuously removed (70°C, 1.19g, 0.04 moles) by distillation. The reaction was monitored using HPLC and after two hours the excess 1-nonanol was removed under vacuum (19.64g, 0.136moles). This resulted in a viscous liquid which solidified on cooling to yield 1-nonyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (12.10g, 0.032moles, 85.41%), melting point 66-67°C. ν max., $3474cm^{-1}$ (NH_2), $2902cm^{-1}$ (CH), 1753 (C=O), $1616\text{-}1416cm^{-1}$ (C=C, C=N ring stretching skeletal bands), $1078cm^{-1}$ (C-F), $763cm^{-1}$ (C-Cl). ^1H NMR spectra δ_H (200MHz; $CDCl_3$): 5.179ppm (broad, 2H, NH_2), 4.865ppm (s, 2H, CH_2,), 4.158ppm (t, 2H, CH_2), 1.620ppm (s, 2H, CH_2), 1.252ppm (s, 12H, $(CH_2)_6$), 0.871ppm (s, 3H, (CH_3). δ_C (50MHz; $CDCl_3$): 168.469ppm (C=O, C_8), 155.294ppm (d, C_6), 154.535ppm (d, C_2), 150.582ppm (d, C_4), 96.946ppm (d, C_3), 93.881ppm (d, C_5), 65.415ppm ($\underline{C}H_2$, C_7), 63.260ppm ($\underline{C}H_2$, C_9), 31.766ppm ($\underline{C}H_2$, C_{15}), 29.361ppm ($\underline{C}H_2$, C_{13}), 29.126ppm ($\underline{C}H_2$, C_{12}), 29.088ppm ($\underline{C}H_2$, C_{14}), 28.413ppm ($\underline{C}H_2$, C_{10}), 25.666ppm ($\underline{C}H_2$, C_{11}), 22.563ppm ($\underline{C}H_2$, C_{16}), 14.013ppm ($\underline{C}H_3$, C_{17}). ClMS 381m/z. Analysis: Found %: C, 50.29; H, 5.99; N, 7.35. Calculated for $C_{16}H_{23}N_2O_3Cl_2F$ %: C, 50.40; H, 6.08; N, 7.347.

3.11 Synthesis of 1-decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate

A mixture of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (7.0g, 0.026 moles) and water (0.7g, 0.039moles) was combined with 1-decanol (19.5g, 0.123 moles) in a 100cm^3 2-neck round bottom flask fitted with a thermometer, still head packed with beads, condenser, vacuum source and magnetic stirrer. The mixture was heated to 150°C and tetrabutyl titanate (catalytic amount) was added. The mixture was then heated to reflux (180°C). The methanol by-product was continuously removed (70°C, 0.832g, 0.028moles) by distillation. The reaction was monitored using HPLC and after two hours the excess 1-decanol was removed under vacuum (15.386g, 0.097moles). This resulted in a viscous liquid which solidified on cooling to yield 1-decyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (5.6g, 0.014moles, 54.4%), melting point 65-65.5°C. ν max., 3371cm^{-1} (NH_2), 2925cm^{-1} (CH), 1748cm^{-1} (C=O), 1622-1444cm^{-1} (C=C, C=N ring stretching skeletal bands), 1090cm^{-1} (C-F), 769cm^{-1} (C-Cl). ^{1}H NMR spectra δ_H (200MHz; $CDCl_3$): 5.174ppm (broad, 2H, NH_2), 4.868ppm (s, 2H, CH_2,), 4.159ppm (t, 2H, CH_2), 1.601ppm (t, 2H, CH_2), 1.252ppm (s, 14H, $(CH_2)_7$), 0.872ppm (s, 3H, (CH_3)). ^{13}C NMR spectra δ_C (50MHz; $CDCl_3$): 168.454ppm (C=O, C_8), 155.287ppm (d, C_6), 154.532ppm (d, C_2), 150.552ppm (d, C_4), 96.947ppm (d, C_3), 93.885ppm(d, C_5), 65.40ppm ($\underline{C}H_2$, C_7), 63.26ppm ($\underline{C}H_2$, C_9), 28.398ppm ($\underline{C}H_2$, C_{10}), 25.659ppm ($\underline{C}H_2$, C_{11}), 29.415ppm ($\underline{C}H_2$, C_{12}), 29.089ppm ($\underline{C}H_2$, C_{13}), 29.218ppm ($\underline{C}H_2$, C_{14}), 29.415ppm ($\underline{C}H_2$, C_{15}), 31.79ppm ($\underline{C}H_2$, C_{16}), 22.587ppm ($\underline{C}H_2$, C_{17}), 14.021ppm ($\underline{C}H_3$, C_{18}). CIMS 395 m/z. Analysis: Found %: C, 51.37; H, 6.41; N, 7.01. Calculated for $C_{17}H_{25}N_2O_3Cl_2F$ %: C, 51.65; H, 6.37; N, 7.08.

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Appendices:

Table A 1

TABLE Alphabetical Listing of Herbicides by Common Name and Corresponding Trade Name, Chemical Name, and Manufacturer

Common name	Trade name[a]	Chemical name	Manufacturer
Acifluorfen	Blazer	5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoic acid	Rohm and Haas
Acrolein	Aquaim	Acrolein (2-propenal)	Shell
Alachlor	Lasso	2-Chloro-2',6'-diethyl-*N*-(methoxymethyl)acetanilide	Monsanto
Allyl alcohol	Allyl Alcohol	Propen-1-ol-3	Shell
AMA	Several	Ammonium methylarsonate	Several
Ametryn	Evik, Gesapax	2-(Ethylamino)-4-(isopropylamino)-6-(methylthio)-*s*-triazine	Ciba-Geigy
Amitrole	Amizol, Amino Triazole, Weedazol	3-Amino-*s*-triazole	American Cyanamid, Union Carbide
AMS	Ammate	Ammonium sulfamate	duPont
Asulam	Asulox	Methyl sulfanilylcarbamate	Rhodia
Atrazine	AAtrex	2-Chloro-4-(ethylamino)-6-(isopropylamino)-*s*-triazine	Ciba-Geigy
Barban	Carbyne	4-Chloro-2-butynyl *m*-chlorocarbanilate	Gulf
Benazolin	Benazolin	4-Chloro-2-oxobenzothiazolin-3yl-acetic acid	Boots
Benefin	Balan	*N*-Butyl-*N*-ethyl-α,α,α-trifluoro-2,6-dinitro-*p*-toluidine	Elanco
Bensulide	Betasan, Prefar	*O,O*-Diisopropyl phosphorodithioate *S*-ester with *N*-(2-Mercaptoethyl)benzenesulfonamide	Stauffer
Bentazon	Basagran	3-Isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide	BASF
Benzadox	Topcide	(Benzamidooxy)acetic acid	Gulf
Bifenox	Modown	Methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate	Mobil
Borate (meta)	Several	Sodium metaborate tetrahydrate	Occidental
Borate (octa)	Polybor	Disodium octaborate tetrahydrate	U.S. Borax
Borax	Several	Sodium tetraborate	Occidental
Bromacil	Hyvar	5-Bromo-3-*sec*-butyl-6-methyluracil	du Pont
Bromoxynil	Brominal, Buctril	3,5-Dibromo-4-hydroxybenzonitrile	Rhodia, Union Carbide
Bulab	Buban	3',5'-Dinitro-4'-(di-*n*-propylamino)acetophenone	Buckman
Butachlor	Machete	*N*-(Butoxymethyl)-2-chloro-2',6'-diethylacetanilide	Monsanto
Butam	GCP-5544	2,2-Dimethyl-*N*-(1-methylethyl)-*N*-(phenylmethyl)propanamide	Gulf
Buthidazole	Ravage	3-[5-(1,1-Dimethylethyl)-1,3,4-thiadiazol-2-yl]-4-hydroxy-1-methyl-2-imidazolidinone	Velsicol
Butralin	Amex, Tamex	4-(1,1-Dimethylethyl)-*N*-(1-methylpropyl)-2,6-dinitrobenzenamine	Union Carbide
Butylate	Sutan	*S*-Ethyl diisobutylthiocarbamate	Stauffer
Cacodylic acid	Rad-E-Cate	Hydroxydimethylarsine oxide	Vineland
Calcium cyanamide	Cyanamide	Calcium cyanamide	American Cyanamid
CDAA	Randox	*N,N*-Diallyl-2-chloroacetamide	Monsanto
CDEC	Vegadex	2-Chloroallyl diethyldithiocarbamate	Monsanto
Chloramben	Amiben, Vegiben	3-Amino-2,5-dichlorobenzoic acid	Union Carbide
Chlorbromuron	Maloran	3-(4-Bromo-3-chlorophenyl)-1-methoxy-1-methylurea	Ciba-Geigy
Chlorflurenol	Maintain	Methyl 2-chloro-9-hydroxyfluorene-9-carboxylate	U.S. Burax
Chloropicrin	Chloropicrin	Chloropicrin	Dow, Monsanto
Chloroxuron	Tenuran	3-[*p*-(*p*-Chlorophenoxy)phenyl]-1,1-dimethylurea	Ciba-Geigy
Chlorpropham	Chloro IPC, Furloe	Isopropyl *m*-chlorocarbanilate	PPG
Copper chelate	Cutrine	Copper II alkanolamine complex	Applied Biochemists

Table A 1 Continued

TABLE (continued)

Common name	Trade name[a]	Chemical name	Manufacturer
Copper sulfate	Copper Sulfate, Bluestone	Copper sulfate pentahydrate	Many
Copper ethylenediamine	Komeen	Copper-ethylenediamine complex	Sandoz
Copper triethanolamine	K-Lox	Copper-triethanolamine complex	Sandoz
Cyanazine	Bladex	2-[[4-Chloro-6-(ethylamino)-*s*-triazin-2-yl]amino]-2-methylpropionitrile	Shell
Cycloate	Ro-Neet	*S*-Ethyl *N*-ethylthiocyclohexanecarbamate	Stauffer
Cyprazine	Outfox	2-Chloro-4-(cyclopropylamino)-6-(isopropylamino)-*s*-triazine	Gulf
Cypromid	Clobber	3,4'-Dichlorocyclopropanecarboxanilide	Gulf
2,4-D	Several	(2,4-Dichlorophenoxy)acetic acid	Many companies
2,4-DB	Butoxone	4-(2,4-Dichlorophenoxy)butyric acid	Rhodia, Union Carbide
Dalapon	Dowpon, Radapon	2,2-Dichloropropionic acid	Dow
Dazomet	Mylone, DMTT	Tetrahydro-3,5-dimethyl-2*H*-1,3,5-thiadiazine-2-thione	Union Carbide
DCPA	Dacthal	Dimethyl tetrachloroterephthalate	Diamond Shamrock
Desmedipham	Betanex	Ethyl *m*-hydroxycarbanilate carbanilate	Nor-Am
Diallate	Avadex	*S*-(2,3-Dichloroallyl)diisopropylthiocarbamate	Monsanto
Dicamba	Banvel	3,6-Dichloro-*o*-anisic acid	Velsicol
Dichlobenil	Casoron	2,6-Dichlorobenzonitrile	Thompson-Hayward
Dichloropicolinate	Lontrel	3,6-Dichloropicolinic acid	Dow
Dichlorprop	Several	2-(2,4-Dichlorophenoxy)propionic acid	Several
Diclofop	Hoelon	2-[4-(2,4-Dichlorophenoxy)phenoxy] propanoic acid	American Hoechst
Diethatyl	Antor	*N*-(Chloroacetyl)-*N*-(2,6-diethylphenyl)glycine	Hercules
Diphenzoquat	Avenge, Finaven	1,2-Dimethyl-3,5-diphenyl-1*H*-pyrazolium	American Cyanamid
Dinitramine	Cobex	N^4,N^4-Diethyl-α,α,α-trifluoro-3,5-dinitrotoluene-2,4-diamine	U.S. Borax
Dinoseb	Several	2-*sec*-Butyl-4,6-dinitrophenol	Dow, FMC
Diphenamid	Enide	*N,N*-Dimethyl-2,2-diphenylacetamide	Upjohn
Dipropetryn	Sancap	2-(Ethylthio)-4,6-*bis*(isopropylamino)-*s*-triazine	Ciba-Geigy
Diquat	Diquat, Reglone	6,7-Dihydrodipyrido[1,2-*a*:2',1'-*c*]pyrazinediium	ICI, Chevron
Diuron	Karmex	3-(3,4-Dichlorophenyl)-1,1-dimethylurea	du Pont
DSMA	Several	Disodium methanearsonate	Several
Endothall	Several	7-Oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid	Pennwalt
EPTC	Eptam	*S*-Ethyl dipropylthiocarbamate	Stauffer
Ethalfluralin	Sonalan	*N*-Ethyl-*N*-(2-methyl-2-propenyl)-2,6-dinitro-4-(trifluoromethyl)benzenamine	Elanco
EXD	Herbisan-5	*O,O*-Diethyl dithio-*bis*(thioformate)	Roberts
Fenac	Fenac	(2,3,6-Trichlorophenyl)acetic acid	Union Carbide
Fenuron-TCA	Urab	1,1-Dimethyl-3-phenylurea mono(trichloroacetate)	Allied
Fluchloralin	Basalin	*N*-(2-Chloroethyl)-2,6-dinitro-*N*-propyl-4-(trifluoromethyl)aniline	BASF
Fluometuron	Cotoran, Lanex	1,1-Dimethyl-3-(α,α,α-trifluoro-*m*-tolyl)urea	Ciba-Geigy, Nor-Am
Fluorodifen	Preforan	*p*-Nitrophenyl α,α,α-trifluoro-2-nitro-*p*-tolyl ether	Ciba-Geigy
Flurenol	Flurenol	*n*-Butyl-9-hydroxyfluorene-(9)-carboxylate	Celamerck
Fluridone	Brake	1-Methyl-3-phenyl-5-[3-(trifluoromethyl)phenyl]-4(1*H*)-pyridinone	Elanco
Fosamine	Krenite	Ethyl hydrogen (aminocarbonyl)phosphonate	du Pont

Table A 2

TABLE A-2. Alphabetical Listing of Herbicides by Trade Name and Corresponding Common Name[a]

Trade names	Common names
AAtrex	Atrazine
Actrilawn	Ioxynil
Alanap	Naptalam
Allyl Alcohol	Allyl alcohol
Amex	Butralin
Amiben	Chloramben
Amino Triazole	Amitrole
Amizol	Amitrole
Ammate	AMS
Ansar	Methanearsonate salts
Antor	Diethatyl
Aqualin	Acrolein
Aquathol	Endothall
Aquazine	Simazine
Asulox	Asulam
Avadex	Diallate
Avadex BW	Triallate
Avenge	Difenzoquat
Balan	Benefin
Balfin	Benefin
Banafine	Benefin
Banvel	Dicamba
Basagran	Bentazon
Basalin	Fluchloralin
Benzac	2,3,6-TBA
Betanal	Phenmedipham
Betanex	Desmedipham
Betasan	Bensulide
Bexton	Propachlor
Bladex	Cyanazine
Blazer	Acifluorfen
Bluestone	Copper sulfate
Bolero	Thiobencarb
Brominal	Bromoxynil
Brush-Rhap	2,4,5-T
Buban 37	Bulab
Buctril	Bromoxynil
Butoxone	2,4-DB
Butyrac	2,4-DB
Calar	CMA
Can-trol	MCPB
Caparol	Prometryn
Carbyne	Barban

TABLE A-2. (continued)

Trade names	Common names
Casoron	Dichlobenil
Chem-hoe	Propham
Chloro IPC	Chlorpropham
Clobber	Cypromid
Cobex	Dinitramine
Conquer	Prometon
Cornox	Dichlorprop
Cotoran	Fluometuron
Cutrine	Copper chelate
Cyanamide	Calcium cyanamide
Daconate	MAA
Dacthal	DCPA
Decamine	2,4,5-T
Destun	Perfluidone
Devrinol	Napropamide
Dowpon	Dalapon
Dual	Metolachlor
Dymid	Diphenamid
Elancolan	Trifluralin
Embark	Mefluidide
Enide	Diphenamid
Eptam	EPTC
Evik	Ametryn
Evital	Norflurazon
Finaven	Difenzoquat
Furloe	Chlorpropham
Garlon	Triclopyr
Gatnon	Benzthiazuron
Gesagard	Prometryn
Gexapax	Ametryn
Gesaprim	Atrazine
Goal	Oxyfluorfen
Gramoxone	Paraquat
Herbadox	Pendimethalin
Herban	Norea
Herbisan-5	EXD
Hyvar	Bromacil
Igran	Terbutryn
Iso-Cornox	Mecoprop

Table A 2

TABLE A-2. (continued)

Trade names	Common names
Karmex	Diuron
Kazoe	Potassium azide
Kerb	Pronamide
K-Lox	Copper-triethanolamine complex
Komeen	Copper-ethylenediamine complex
Krenite	Fosamine
Kuron	Silvex
Lanex	Fluometuron
Lasso	Alachlor
Lexon	Metribuzin
Lontrel	3,6-Dichloropicolinic acid
Lorox	Linuron
Lo-Vol	2,4,5-T
Machete	Butachlor
Maintain	Chlorfluorenol
Maloran	Chlorbromuron
Milogard	Propazine
Modown	Bifenox
Mylone	Dazomet
Nopalmate	Hexaflurate
Ordram	Molinate
Outfox	Cyprazine
Paarlan	Isopropalin
Planavin	Nitralin
Pramitol	Prometon
Prebane	Terbutryn
Prefar	Bensulide
Premerge	Dinoseb
Preforan	Fluorodifen
Princep	Simazine
Probe	Methazole
Prowl	Pendimethalin
Pyramin	Pyrazon
Quilan	Bencfin
Radapon	Dalapon
Rad-E-Cate	Cacodylic acid
Ramrod	Propachlor
Randox	CDAA
Ravage	Buthidazole

Table A 2

TABLE A-2. (continued)

Trade names	Common names
Reglone	Diquat
Rhomene	MCPA
Rhonox	MCPA
Ro-neet	Cycloate
Ronstar	Oxadiazon
Roundup	Glyphosate
Rydex	Prodiamine
Ryzelan	Oryzalin
Sancap	Dipropetryn
Saturn	Thiobencarb
Sencor	Metribuzin
Sinbar	Terbacil
Smite	Sodium azide
Solicam	Norflurazon
Sonalan	Ethalfluralin
Spike	Tebuthiuron
Stam	Propanil
Stomp	Pendimethalin
Sumitol	Secbumeton
Surflan	Oryzalin
Sutan	Butylate
Sward	Prosulfalin
Tamex	Butralin
Tandex	Karbutilate
Tenoran	Chloroxuron
Tillam	Pebulate
Tinistrol	MCPB
Tok	Nitrofen
Tolban	Profluralin
Topcide	Benzadox
Tordon	Picloram
Totril	Ioxynil
Trans-Vert	MMA
Trefanocide	Trifluralin
Treflan	Trifluralin
Trysben	2,3,6-TBA
Tupersan	Siduron
Urab	Fenuron-TCA
Urox	Monuron-TCA
Vapam	Metham
Vegadex	CDEC

Table A 2

TABLE A-2. (continued)

Trade names	Common names
Vegiben	Chloramben
Velpar	Hexazinone
Veon	2,4,5-T
Vernam	Vernolate
Vipex	Mecoprop
Vorlex	Vorlex
Weedazol	Amitrole
Weed-E-Rad	MAA
Weed-Hoe	MAA
Zorial	Norflurazon

[a]Trade names of combinations of two or more herbicides are not given; for these see *Herbicide Handbook*, 4th Ed., 1979. Weed Science Society of America. Champaign, Illinois.

Table A 3

TABLE Herbicides: Chemical Classification

Inorganic Herbicides

AMS
Borate (meta)
Borate (octa)
Borax
Calcium cyanamide
Copper chelate[a]
Copper-ethylenediamine[a]
Copper sulfate
Copper-triethanolamine[a]
Hexaflurate
Potassium azide
Sodium azide
Sodium chlorate
Sulfuric acid

Organic Herbicides

1. Aliphatics
   - A. Chlorinated acids
     - Dalapon
     - TCA
   - B. Organic arsenicals
     - Cacodylic acid
     - DSMA
     - MAA
     - MAMA
     - MSMA
   - C. Others
     - Acrolein
     - Allyl alcohol
     - Methyl bromide
     - Glyphosate
2. Amides
   - A. Chloroacetamides
     - Alachlor
     - Butachlor
     - CDAA
     - Metolachlor
     - Propachlor
     - Terbuchlor
   - B. Others
     - Benzadox
     - Butam
     - Cisanilide
     - Cypromid
     - Diphenamid
     - Napropamide
     - Naptalam
     - Pronamide
     - Propanil
3. Benzoics
   - Chloramben
   - Dicamba
   - 2,3,6-TBA
   - PBA
4. Bipyridiliums
   - Diquat
   - Paraquat
5. Carbamates
   - Asulam
   - Barban
   - Chlorpropham
   - Desmedipham
   - Phenmedipham
   - Propham
6. Dinitroanilines
   - Benefin
   - Butralin
   - Dinitramine
   - Nitralin
   - Oryzalin
   - Pendimethalin

Table A 3

TABLE (continued)

6.	Dinitroanilines (continued)	
	Ethalfluralin	Prodiamine
	Fluchloralin	Profluralin
	Isopropalin	Prosulfalin
		Trifluralin
7.	Diphenyl ethers	
	Acifluorfen	Nitrofen
	Bifenox	Nitrofluorfen
	Diclofop	Oxyfluorfen
	Fluorodifen	
8.	Nitriles	
	Bromoxynil	Ioxynil
	Dichlobenil	
9.	Phenoxys	
	2,4-D	MCPB
	2,4-DB	Dichlorprop
	2,4,5-T	Mecoprop
	MCPA	Silvex
10.	Thiocarbamates	
	Butylate	Thiobencarb
	Cycloate	Triallate
	Diallate	Vernolate
	EPTC	CDEC[b]
	Molinate	Metham[b]
	Pebulate	
11.	Triazines	
	Ametryn	Prometryn
	Atrazine	Propazine
	Cyanazine	Secbumeton
	Cyprazine	Simazine
	Desmetryn	Simetryn
	Dipropetryn	Terbuthylazine
	Procyanzine	Terbutryn
	Prometon	Metribuzin[c]
12.	Uracils	
	Bromacil	Terbacil
	Lenacil	
13.	Ureas	
	Chlorbromuron	Linuron
	Chloroxuron	Monolinuron
	Cycluron	Monuron
	Diuron	MonuronTCA
	Fenuron	Neburon
	FenuronTCA	Norea
	Fluometuron	Siduron
	Karbutilate[d]	Tebuthiuron

Table A 3 continued

14. Unclassified

	Fenac
Amitrole	Flurenol
Benazolin	Fluridone
Bensulide	Hexazinone
Bentazon	Methazole
Bulab	MH
Chlorflurenol	Norflurazon
DCPA	Oxadiazon
3,6-Dichloropicolinic acid	Perfluidone
Diethatyl	Picloram
Difenzoquat	Pyrazon
Dinoseb	Triclopyr
Endothall	Vorlex

[a]Although these complexes are organic in nature, the active ingredient is the copper ion.

[b]Dithiocarbamates

[c]All are symmetrical triazines except metribuzin, which is asymmetrical.

[d]Also contains carbamate group.

Table A 4

This table organizes herbicides into those which are applied to foliage (many of these are applied to soil as well) and those herbicides applied almost strictly to soil. The foliar applied groups are then divided into three categories according to movement through the plant:
1) symplastically translocated (source to sink capable of downward movement),
2) apoplastically translocated (capable of only upward movement),
3) those which do not move appreciably (kill very quickly).
Each translocation group is subdivided into mode-of-action groups which are further categorized by herbicide chemistry group. Strictly soil applied herbicides are divided into mode-of-action and then into herbicide chemistry groups.

I. Foliar Applied Herbicides
A. Downwardly Mobile Herbicides [Symplastically Translocated (leaf to growing points)]

1. Auxin Growth Regulators

Common Name	Trade Name
Phenoxyaliphatic Acid Herbicides	
2,4-D	
2,4-DB	
MCPP	(mecoprop)
MCPA	
2,4-DP	(dichlorprop)
Benzoic Acids	
dicamba	BANVEL/ CLARITY/ VANQUISH/ VETERAN
Picolinic Acids (Pyridines) and Relatives	
picloram	TORDON
clopyralid	STINGER/ LONTREL
triclopyr	GARLON/ TURFLON
fluroxypyr	STARANE

2. Amino Acid Inhibitors (Aromatic)

Common Name	Trade Name
glyphosate	ROUNDUP ULTRA/ RODEO/ACCORD
sulfosate	TOUCHDOWN

3. Amino Acid Inhibitors [Branched-chain (AHAS/ALS)]

Imidazolinones

Common Name	Trade Name
imazquin	SCEPTER
imazethapyr	PURSUIT
imazapyr	ARSENAL/ CHOPPER

Sulfonylureas

Common Name	Trade Name
chlorimuron	CLASSIC
chlorsulfuron	GLEAN/ TELAR
nicosulfuron	ACCENT
primisulfuron	BEACON
thifensulfuron	HARMONY PINNACLE
tribenuron	EXPRESS
sulfometuron	OUST
metsulfuron	PERMIT/ MANAGE

Sulfonanilides

flumetsulam	BROADSTRIKE

4. Chlorophyll/Carotenoid Pigment Inhibitors

Common Name	Trade Name
clomazone	COMMAND
amitrole	AMITROL-T
norflurazon	ZORIAL/ SOLICAM
fluridone	SONAR

5. Grass Meristem Destroyers (Lipid Biosynthesis Inhibitors)

Aryloxyphenoxypropionates

Common Name	Trade Name
fenoxaprop	WHIP/ HORIZON/ OPTION/ ACCLAIM
fluazifop-P	FUSILADE 2000/ FUSILADE DX
quizalofop	ASSURE II

Cyclohexanediones

clethodim	SELECT
sethoxydim	POAST/ POAST PLUS

B. Non Translocated (Contact Herbicides)

Bipyridyliums

Common Name	Trade Name
paraquat	GRAMOXONE
diquat	DIQUAT/REWARD

Diphenyl ethers (nitrophenyl ethers)

Common Name	Trade Name
acifluorfen	BLAZER
fomesafen	REFLEX
lactofen	COBRA
oxyfluorfen	GOAL

Other postemergence herbicides

Common Name	Trade Name
bentazon	BASAGRAN
glufosinate	IGNITE/RELY/ FINALE/LIBERTY

C. Upwardly Mobile Only Herbicides (Apoplastically Translocated)
Photosynthetic Inhibitors

Triazines

Common Name	Trade Name
atrazine	AATREX/Atrazines
simazine	PRINCEP
cyanazine	BLADEX
prometon	PRAMITOL
metribuzin	SENCOR/LEXONE
hexazinone	VELPAR

Uracils

terbacil	SINBAR
bromacil	HYVAR

Phenylureas

linuron	LOROX/LINEX
diuron	KARMEX
tebuthiuron	SPIKE

II. Soil Applied Herbicides

Root Inhibitors

Dinitrroanilines

Common Name	Trade Name
trifluralin	TREFLAN
benefin	BALAN
prodiamine	BARRICADE/ ENDURANCE
oryzalin	SURFLAN
pendimethalin	PROWL/PENTAGON STOMP/PENDULUM
ethalfluralin	SONALAN

Miscellaneous Herbicides

Common Name	Trade Name
DCPA	DACTHAL
siduron	TUPERSAN

2. Shoot Inhibitors

Thiocarbamates (Carbamothioates)

Common Name	Trade Name
EPTC	EPTAM/ERADICANE
butylate	SUTAN+
pebulate	TILLAM
cycloate	RO-NEET

Substituted Amides (Chloroacetamides)

Common Name	Trade Name
acetochlor	HARNESS/SURPASS/ TOPNOTCH
alachlor	LASSO/MICRO-TECH/PARTNER
metolachlor	DUAL/DUAL II
propachlor	RAMROD
dimethenamid	FRONTIER

3. Shoot and Root Inhibitors

Common Name	Trade Name
bensulide	BETASAN/ BENSULIDE/PREFAR
napropamide	DEVRINOL
pronamide	KERB
dichlobenil	CASORON
dithiopyr	DIMENSION